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(54) **Processes for the production of 13-ether derivatives of milbemycins, and intermediates therefor**

Verfahren zur Herstellung von 13-Ether-Derivaten von Milbemycinen und Zwischenprodukte

Procédés pour la préparation de dérivés des milbémycines ayant un groupe éther en position 13

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Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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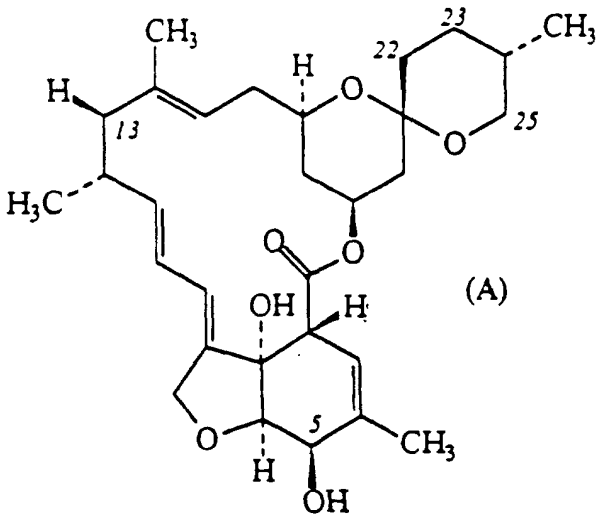
Description

[0001] The present invention relates to novel processes for the preparation of 13-ether derivatives of milbemycins, and to novel intermediates for use in such processes.

[0002] There are several classes of known compounds with a structure based on a 16-membered macrolide ring, which compounds are obtained by fermentation of various microorganisms or are obtained semi-synthetically by chemical derivatisation of such natural fermentation products, and which exhibit acaricidal, insecticidal, anthelmintic and antiparasitic activities. The milbemycins are one such class.

[0003] In order to avoid confusion, a standardised system of nomenclature for the milbemycins will be used herein, which follows the normal rules for naming derivatives of organic compounds as recommended by the International Union of Pure and Applied Chemistry, Organic Chemistry Division, Commission on Nomenclature of Organic Chemistry, and which is based primarily on the hypothetical parent compound hereby defined as "milbemycin" and represented by the formula (A) :



[0004] For the avoidance of doubt, formula (A) also shows the numbering of positions of the macrolide ring system applied to those positions most relevant to the compounds of the present invention and of the prior art.

[0005] The naturally produced milbemycins are a series of macrolide compounds known to have anthelmintic, acaricidal and insecticidal activities. Milbemycin D was disclosed in US Patent No. 4,346,171, where it was referred to as "Compound B-41D", and milbemycins A_3 and A_4 were disclosed in US Patent No. 3,950,360. These compounds may be represented by the above formula (A) in which there is a hydrogen atom at position 13 and position 25 is substituted with a methyl group, an ethyl group or an isopropyl group, these compounds being designated as milbemycin A_3, milbemycin A_4 and milbemycin D, respectively.

[0006] 13-Hydroxy-5-ketomilbemycin derivatives have been disclosed in US Patent No. 4,423,209, and milbemycin 5-oxime derivatives have been disclosed in US Patent No. 4,547,520 and in European Patent Publication No. 203 832.

[0007] Milbemycins having an ether group at the 13-position have been found to have various useful activities, including particularly strong anthelmintic activity in cattle, for example. The nature of the ether group is not particularly important but it is generally an alkoxy, alkenyloxy, alkynyloxy or aralkoxy group, the substituted phenylalkoxy groups, particularly the phenethoxy group, being most preferred. For example, European Patent Publication No. 357 460 discloses milbemycin derivatives having an optionally substituted phenethoxy group at the 13-position, these compounds having excellent anthelmintic activity.

[0008] However, the problem with the 13-ether substituted milbemycins is that there is no commercially viable process for their production. The processes which are described for the production of these compounds in the prior art necessarily employ toxic and/or expensive metal catalysts.

[0009] The prior art processes essentially fall into two categories, and the two types of prior art process which are generally used in the manufacture of 13-ether substituted milbemycins involve either:

1) Reacting a milbemycin having a leaving group, such as iodine, in the 13-position with an appropriate alcohol in the presence of a catalyst; or

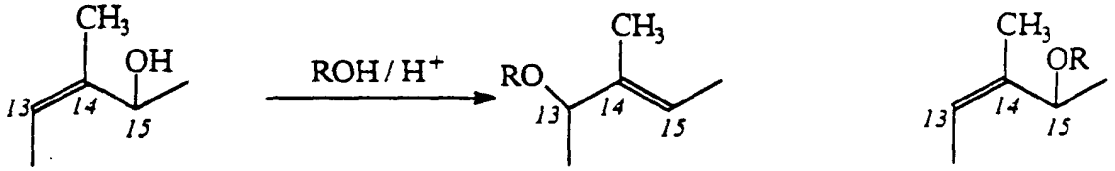
2) Reacting a 15-hydroxy substituted milbemycin derivative with an appropriate alcohol in the presence of an acid.

[0010] In the case of 1) above, a suitable process is described in Japanese Unexamined Patent Publication No. Hei-2-174780, corresponding to European Patent Publication No. 357 460.

[0011] In the case of 2) above, a suitable process is described in Japanese Unexamined Patent Publication No. Sho-61-178986, corresponding to US Patent No. 4,696,945.

[0012] With regard to process 1), the catalysts employed are the oxides or salts of silver or mercury. Silver catalysts are very expensive to use in bulk manufacturing operations, even when it is possible to recover the catalyst from the final product. On the other hand, mercury is toxic, and care must be exercised to ensure that all mercury is removed from the final product.

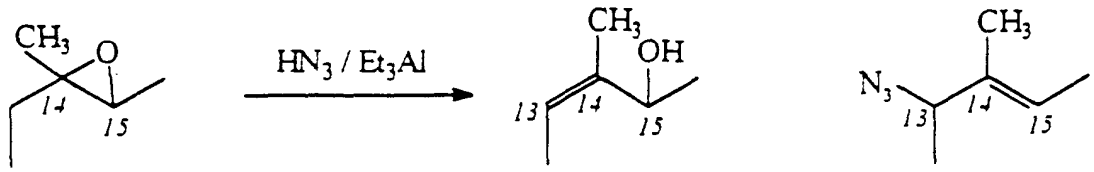
[0013] With regard to process 2), there are two main problems. The first problem lies in the reaction of the 15-hydroxy compound with the alcohol. The reaction scheme with partial formulae is as shown below:



(a) (b) (c)

It can be seen that the reaction of the 15-hydroxy compound of partial structure (a) with alcohol yields a mixture of products (b) and (c). In addition, the starting compound must also be protected at the 5-hydroxy position before the reaction can be performed.

[0014] The second, more serious problem, with process 2) is concerns the manufacture of the starting material (a). Japanese Unexamined Patent Publication No. Sho 60-158191, (corresponding to European Patent Publication No. 147852), and Helvetica Chimica Acta, 73, 1905 (1990), describe a process wherein the 15-hydroxy compound (a) can be obtained by treating a 14,15-epoxy compound (d) with a mixture of hydrogen azide and triethylaluminum. The reaction scheme with partial formulae is as follows:



(d) (a) (e)

[0015] From the above reaction scheme, it can be seen that the compound of formula (a) is obtained together with the 14-azide compound (e). The hydrogen azide used in this process is highly toxic and dangerous (Shin-Jikken Kagaku Kouza, 8, pp. 327 and 328, compiled by Japan Chemical Association, published by Maruzen, December 20, 1976). Triethyl aluminum is also dangerous, because it ignites when brought into contact with water or air, even at room temperature (Shin-Jikken Kagaku Koza, 12, p. 308, compiled by Japan Chemical Association, published by Maruzen, issued on March 20, 1976). Furthermore, as is well known with dry azide compounds (Shin-Jikken Kagaku Koza, 14, p. 1660, compiled by Japan Chemical Association, published by Maruzen, February 20, 1978), there is a danger of the 14-azide compound (e) exploding if exposed to heat or mechanical shock. Thus, the known method for preparing the starting material of formula (a) is not only impractical but also dangerous for bulk manufacturing operations.

[0016] Japanese Patent Application No. Hei-3-258036, published in May, 1993 and Japanese patent application JP-A-05097860, published in April 1993, disclose processes for preparing 13-substituted milbemycin derivatives starting from a 5-hydroxy milbemycin compound. Japanese patent application no. JP-A-05097859, published in April 1993, discloses a 15-hydroxymilbemycin derivative and its use for the preparation of 13-substituted milbemycin derivatives.

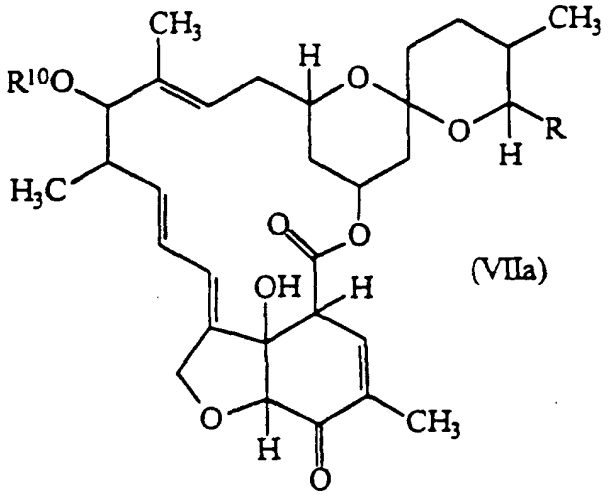
[0017] EP-A-0448243 and EP-A-0444964 disclose 13-ether milbemycin derivatives and processes for their produc-

tion. EP-A-0288205 discloses 5-hydroxy and 5-alkoxy milbemycin derivatives and processes for their production. JP-A-05097863, which was published in April 1993, discloses 5,15-dihydroxymilbemycin derivatives and a process for their production from a 14,15-epoxy derivative.

[0018] It is an object of the present invention to provide a novel process for the manufacture of 13-substituted milbemycins. It is a further object to provide a process for the manufacture of 13-substituted milbemycins which is safe and cheap to use on a commercial scale. It is a yet further object to provide a method of manufacture of 13-substituted milbemycins which uses a minimal number of reaction steps. It is also an object to provide novel milbemycin derivatives for use in a method of manufacture of 13-substituted milbemycins.

[0019] We have now discovered that it is possible to synthesise 13-ether substituted milbemycins from a 5-oxomilbemycin derivative and thereby overcome the above problems.

[0020] The invention provides a process for the preparation of a compound of formula (VIIa) :

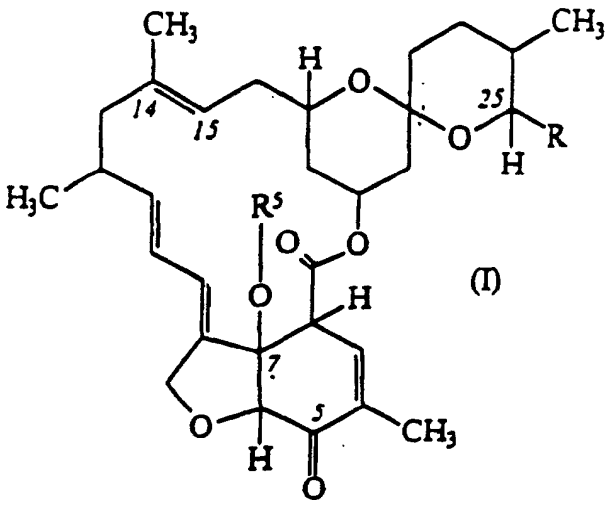


(VIIa)

wherein R represents a methyl group, an ethyl group, an isopropyl group or a sec-butyl group, and R^{10} represents an alkyl group having from 1 to 20 carbon atoms; an alkenyl group having from 2 to 6 carbon atoms; an alkynyl group having from 2 to 6 carbon atoms; or an aralkyl group in which the alkyl part has from 1 to 10 carbon atoms and which may be unsubstituted or substituted by 1 or 2 alkoxy groups each having from 1 to 4 carbon atoms, and the aryl part has from 6 to 10 ring carbon atoms and is substituted by at least one of the substituents defined below for R^{11} and R^{12} or unsubstituted,

which process comprises the steps:

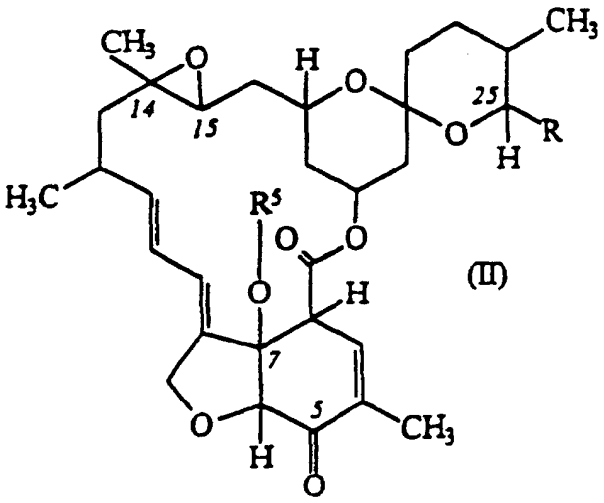
A. epoxidising a compound of formula (I) using a reagent system comprising effective amounts of potassium peroxymonosulphate and one or more ketones:



(I)

wherein R is as defined above and R^5 represents a hydrogen atom or a group of formula $-SiR^2R^3R^4$, in which R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 6 carbon atoms;

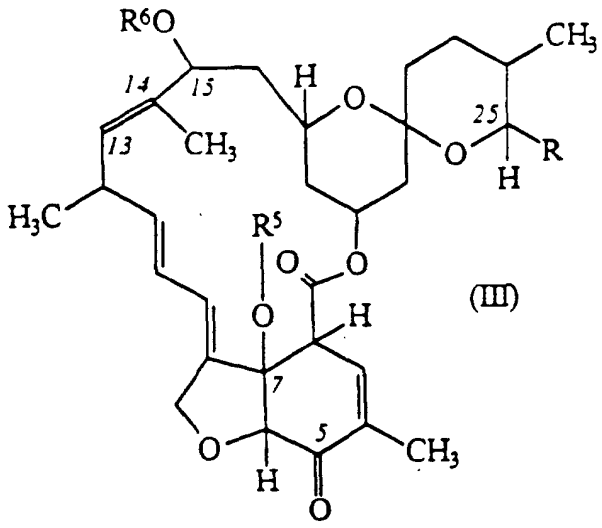
to give a compound of formula (II) :



(II)

wherein R and R^5 are as defined above;

B. subjecting the resulting compound of formula (II) to a ring-opening etherification reaction to give a compound of formula (III) :



wherein R and R^5 are as defined above and R^6 represents a group of formula $-SiR^7R^8R^9$, wherein R^7, R^8 and R^9 are each independently selected from alkyl groups having from 1 to 6 carbon atoms, phenyl groups and benzyl groups;

and

C. reacting the resulting compound of formula (III) with a compound of formula $R^{10}OH$ to give said compound of formula (VIIa).

[0021] Each of the above steps, individually, also forms a part of the invention.

[0022] The present invention also provides novel intermediates which can be used in the above process.

[0023] Compounds of formula (I) wherein R represents a hydrogen atom are disclosed in Japanese Unexamined Patent Publication No. Hei-1-197487, but use such compounds in the manufacture of 13-substituted milbemycins has not previously been described. In the present invention, the advantage of using such compounds lies in the fact that it is not necessary to protect the 5-hydroxyl group, as in the prior art. Further, as the processes of the prior art first protect the 5-hydroxyl and then eventually result in the production of a 5-oxo group, conventional procedures, such as are described in Japanese Patent Application Sho-62-70379, can be employed in the process of the present invention to hydrogenate the 5-oxo group, thereby restoring the original 5-hydroxy group.

[0024] The process of the present invention allows 13-ether milbemycins to be obtained on an industrial scale, in fewer process steps and in higher yields than when compared with conventional reaction processes, without having to employ toxic or dangerous reagents and also without producing potentially dangerous by-products.

[0025] The present invention is particularly suitable for the production of milbemycin derivatives having an optionally substituted phenethyl ether bond at the 13-position, and particularly preferred compounds are described in more detail below.

[0026] In the general formulae above, the preferred meaning for R is methyl or ethyl, more preferably ethyl.

[0027] Step A of the process of the invention epoxidises a compound of formula (I) to yield a compound of formula (II). If desired, a compound of formula (I) wherein R^5 represents a hydrogen atom may first be protected to provide a compound of formula (I) wherein R^5 represents a group of formula $-SiR^2R^3R^4$, wherein R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 6, preferably from 1 to 4 carbon atoms. Examples include trimethylsilyl, triethylsilyl, isopropyldimethylsilyl, t-butyldimethylsilyl, methyldiisopropylsilyl, methyldi-t-butylsilyl and triisopropylsilyl groups.

[0028] Suitable alkyl groups having from 1 to 6 carbon atoms include straight or branched chain groups, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, hexyl and isohexyl groups. Of these, we prefer those alkyl groups having from 1 to 4 carbon atoms, preferably the methyl, ethyl, propyl, isopropyl, butyl and isobutyl groups, and most preferably the t-butyl and methyl groups, particularly methyl groups.

[0029] The optional protection reaction of step A can be performed. However, we have discovered that the use of Oxone (trade mark, potassium peroxymonosulphate) in combination with one or more ketones as the epoxidising agent

results in protection not being required, as there is little or no side reaction at the 7- position. In fact, when Oxone/ ketones are used, conversion to the desired epoxy compound appears to be substantially stoichiometric.

[0030] It will be appreciated that, although Oxone/ ketones are used, the 7- position may be protected, but is not preferred, for the above reasons.

[0031] In step B of the process of the invention, the epoxy group of the compound of formula (II) is ring-opened with etherification to give the compound of formula (III), which has a protecting group R^6 at the 15- position.

[0032] R^6 represents a group of formula $-SiR^7R^8R^9$, wherein R^7, R^8 and R^9 are each independently selected from alkyl groups having from 1 to 6, preferably 1 to 4 carbon atoms, phenyl groups and benzyl groups.

[0033] In general, when R^5 or R^6 represents a tri-substituted silyl group, then the trimethylsilyl group is most preferred.

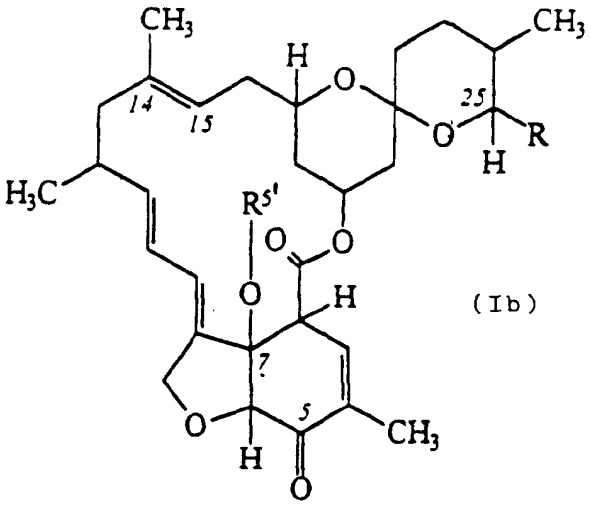
[0034] Subsequent to step B and before step C, the protecting group at the 15- position may be removed to give the 15-hydroxyl milbemycin derivative. This compound may then be used in step C, or may be used to provide further milbemycin derivatives, for example. It will be appreciated that deprotection of the compound of formula (III) is not a preferred step in the process of the invention, as step C can be performed even when the 15- position is protected.

[0035] In step C of the process of the invention, the compound of formula (III) undergoes an etherification reaction under conditions which simultaneously deprotect the compound of formula (III) and enable the appropriate alcohol to form an ether group at the 13- position. Suitable conditions are described hereinafter.

Subsequent hydrogenation with a mild reducing agent, such as sodium borohydride, restores the 5-hydroxyl group to give the desired end-product.

[0036] It will be appreciated that, because the process of the invention is new and starts with a compound not previously described in connection with the preparation of 13-substituted milbemycins, then the intermediates of the process of the invention are also new. Thus, the present invention also provides the intermediates defined above, and as detailed below:

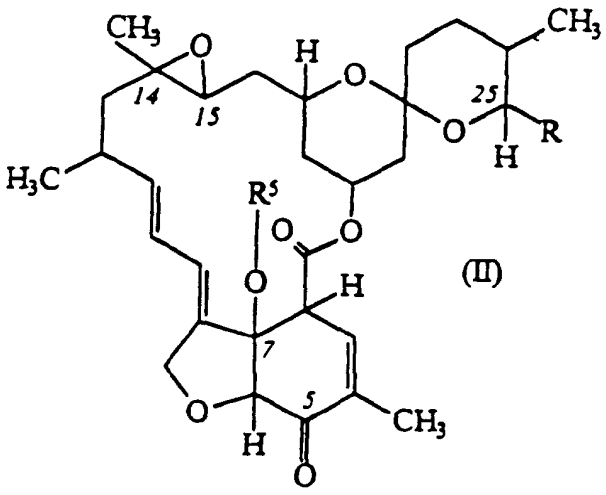
A) Compounds of formula (Ib) :



(Ib)

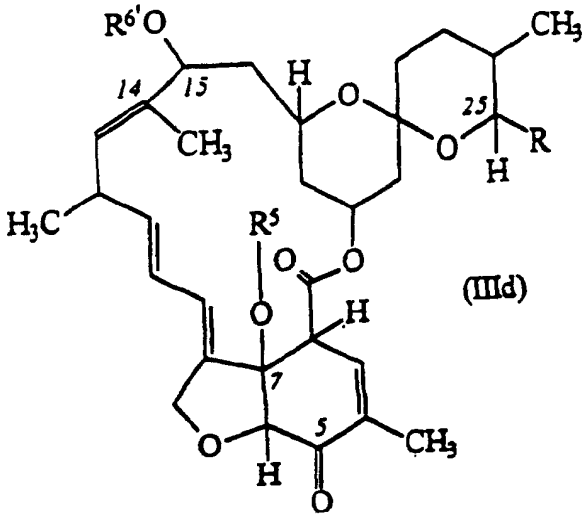
wherein R is as defined above and $R^{5'}$ represents a group of formula $-SiR^2R^3R^4$, wherein R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 6 carbon atoms;

B) Compounds of formula (II) :



wherein R and R^5 are as defined above;

C) Compounds of formula (IIId) :



wherein R is as defined above, R^5 represents a group of formula $-SiR^2R^3R^4$ wherein R^2, R^3 and R^4 each independently represent an alkyl group having from 1 to 4 carbon atoms and $R^{6'}$ represents a hydrogen atom or a group of formula $-SiR^7R^8R^9$, wherein R^7, R^8 and R^9 are each independently selected from alkyl groups having from 1 to 6 carbon atoms, phenyl groups and benzyl groups.

[0037] In the compounds of formula (VIIa), where R^{10} represents an alkyl group, this may be a straight or branched chain group having from 1 to 20, preferably from 1 to 6, carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl, dodecyl, tridecyl, pentadecyl, octadecyl, nonadecyl and icosyl groups, but most preferably the methyl, ethyl and t-butyl groups.

[0038] Where R^{10} represents an alkenyl group, this may be a straight or branched chain group having from 2 to 6, preferably 3 or 4, carbon atoms, and examples include the vinyl, allyl, methallyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl groups, of which the vinyl, allyl, methallyl, 1-propenyl, isopropenyl and butenyl groups are preferred, the allyl and 2-butenyl groups being most preferred.

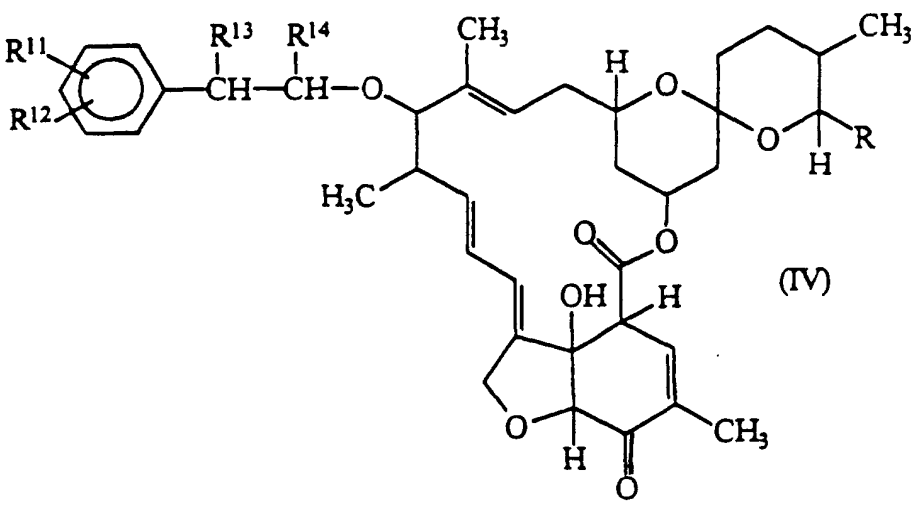
[0039] Where R^{10} represents an alkynyl group, this may be a straight or branched chain group having from 2 to 6, preferably 3 or 4, carbon atoms, and examples include the ethynyl, propargyl (2-propynyl), 1-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl groups, of which the propynyl and butynyl groups are preferred, the propargyl and 2-butynyl groups being most preferred.

[0040] Where R^{10} represents an aralkyl group, the alkyl part preferably has from 1 to 10 carbon atoms and may be unsubstituted or substituted by 1 or 2 alkoxy groups each having from 1 to 4 carbon atoms. The aryl part may have from 6 to 10, preferably 6 or 10, ring carbon atoms and may be unsubstituted or substituted by at least one, preferably from 1 to 5, and more preferably 1 or 2, substituents selected from the groups and atoms defined below for R^{11} and R^{12}. Examples of such aralkyl groups include: unsubstituted groups, such as the benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, a-naphthylmethyl, ö-naphthylmethyl, diphenylmethyl, triphenylmethyl, a-naphthyldiphenylmethyl and 9-anthrylmethyl groups; and substituted groups, including those substituted on the aryl part with a lower alkyl group, a lower alkoxy group, a nitro group, a halogen atom, a cyano group, or an alkylenedioxy group having from 1 to 3 carbon atoms, preferably a methylenedioxy group, such as the 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenyldiphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzoyl, 4-bromobenzyl, 4-cyanobenzyl, 4-cyanobenzyldiphenylmethyl, bis (2-nitrophenyl)methyl and piperonyl groups.

[0041] More preferably, however, the aralkyl group represented by R^{10} is a phenethyl group in which each carbon atom of the alkyl part is substituted by a group or atom R^{13} or R^{14} and the aryl group is substituted by R^{11} and R^{12}, all as defined below.

[0042] We most prefer that R^{10} represents a 4-(N-methanesulphonyl-N-methylamino)phenylethoxy group.

[0043] The compounds which can be prepared by the process of the invention are generally as defined above, but the preferred class of compounds is that having the formula (IV) :



(IV)

in which:

R is as defined above;

R^{11} and R^{12} are independently selected from: hydrogen atoms; halogen atoms; cyano groups; nitro groups; C_1 - C_4 alkyl groups; substituted C_1 - C_4 alkyl groups having at least one substituent selected from substituents (a), defined below; C_1 - C_4 alkoxy groups; C_2 - C_6 alkoxyalkoxy groups; groups of formula $-(CH_2)_nNHR^{19}$,

in which: n represents 0 or the integer 1 or 2, and R^{19} represents a hydrogen atom or a C_1 - C_4 alkyl group;

groups of formula $-(CH_2)_nNR^{19}C(=O)R^{16}$,

in which:

n and R^{19} are as defined above, and

R^{16} represents: a hydrogen atom; a C_1 - C_4 alkyl group; a substituted C_1 - C_4 alkyl group having at least one substituent selected from substituents (b), defined below; a C_2 - C_8 aliphatic hydrocarbon group having

one or two ethylenically unsaturated carbon-carbon double bonds, said group being unsubstituted or having at least one substituent selected from substituents (b), defined below; a C_2 - C_8 alkynyl group; a substituted C_2 - C_8 alkynyl group having at least one substituent selected from substituents (b), defined below; a C_3- C_8 cycloalkyl group; a substituted C_3- C_8 cycloalkyl group having at least one substituent selected from substituents (c), defined below; a carbocyclic aryl group having from 6 to 14 ring carbon atoms and being unsubstituted or having at least one substituent selected from substituents (c), defined below; or a heterocyclic group having from 3 to 6 ring atoms of which at least one is a hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms, said heterocyclic group being monocyclic or fused to one or two benzene rings and being unsubstituted or having at least one substituent selected from substituents (c), defined below;

groups of formula $-(CH_2)_nNR^{19}COCOR^{16}$
in which n, R^{16} and R^{19} are as defined above;

groups of formula $-(CH_2)_nR^{19}COCOOR^{17}$
in which n and R^{19} are as defined above and R^{17} represents a C_1 - C_4 alkyl group, a C_3 - C_8 cycloalkyl group or an aralkyl group as defined below;

groups of formula $-(CH_2)_nNR^{19}CHR^{16}NHCOR^{16}$
in which n, R^{16} and R^{19} are as defined above;

groups of formula $-(CH_2)_nNR^{19}CHR^{16}NHCONHR^{16}$
in which n, R^{16} and R^{19} are as defined above;

groups of formula $-(CH_2)_nNR^{19}CHR^{16}NHCOOR^{17}$
in which n, R^{16}, R^{17} and R^{19} are as defined above;

groups of formula $-(CH_2)_nNR^{19}C(=Y)YR^{16}$
in which n, R^{16} and R^{19} are as defined above and the two symbols Y are independently selected from oxygen and sulphur atoms;

groups of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16'}R^{16'}$
in which n, Y and R^{19} are as defined above, and the two symbols $R^{16'}$ are independently selected from R^{16}, or the two, together with the nitrogen atom to which they are attached, form a heterocyclic group having from 3 to 7 ring atoms of which one is said nitrogen atom and 0 or 1 is an additional hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms;

groups of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16''}NR^{16''}R^{16''}$
in which n, Y and R^{19} are as defined above, and each of the symbols $R^{16''}$ is independently selected from R^{16}, or any two of the symbols $R^{16''}$, together with the nitrogen atom to which each is attached, forms a heterocyclic group having from 3 to 7 ring atoms of which one or two is said nitrogen atom or atoms and 0 or 1 is an additional hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms;

groups of formula - $(CH_2)_nNP^{19}C(=Y)NR^{16}NHZ$
in which n, Y, R^{16} and R^{19} are as defined above and Z represents
a group of formula $-COOR^{17}$, in which R^{17} is as defined above,
a group of formula $-COR^{16}$, in which R^{16} is as defined above, or
a group of formula $-SO_2R^{16}$, in which R^{16} is as defined above;

groups of formula $-(CH_2)_nNR^{19}C(=NR^{20})NHR^{20}$
in which n and R^{19} are as defined above and the two symbols R^{20} are independently selected from R^{16}, cyano groups, nitro groups, groups of formula $-COOR^{17}$, in which R^{17} is as defined above, and groups of formula $-COR^{16}$, in which R^{16} is as defined above;

groups of formula $-(CH_2)_nNR^{19}C(=NR^{20})R^{16}$
in which n, R^{16}, R^{19} and R^{20} are as defined above;

groups of formula $-(CH_2)_nNR^{19}SO_mR^{16}$
in which n, R^{16} and R^{19} are as defined above and m is 1 or 2;

groups of formula -CONHR^{16}
in which R^{16} is as defined above; and

groups of formula -COOR^{17}
in which R^{17} is as defined above;

R^{13} and R^{14} are independently selected from hydrogen atoms, C_1 - C_4 alkyl groups and C_1 - C_4 alkoxy groups; and

said aralkyl groups have from 1 to 4 carbon atoms in the alkyl part and from 6 to 10 ring atoms in the aryl part, which is a carbocyclic aryl group which is unsubstituted or has at least one substituent selected from substituents (c), defined below;

substituents (a) :
halogen atoms, C_1 - C_4 alkoxy groups, C_1 - C_4 alkylthio groups and C_1 - C_5 alkanoyloxy groups;

substituents (b) :
C_3 - C_8 cycloalkyl groups; C_1 - C_4 alkoxy groups; C_1 - C_4 alkylthio groups; C_2 - C_5 cyanoalkylthio groups; C_2 - C_5 alkoxycarbonyl groups; halogen atoms; cyano groups; nitro groups; amino groups; carbocyclic aryl groups having from 6 to 10 carbon atoms and being unsubstituted or having at least one substituent selected from substituents (c), defined below; aromatic heterocyclic groups having from 5 to 8 ring atoms of which from 1 to 4 are hetero-atoms selected from nitrogen, oxygen and sulphur hetero-atoms, said heterocyclic group being monocyclic or fused either to a benzene ring or to a heterocyclic group which has 5 or 6 ring atoms of which from 1 to 3 are nitrogen hetero-atoms and being unsubstituted or having at least one substituent selected from substituents (c), defined below; and aryloxy and arylthio groups in which the aryl part has from 6 to 10 carbon atoms and is unsubstituted or has at least one substituent selected from substituents (c), defined below;

substituents (c) :
C_1 - C_4 alkyl groups, C_1 - C_4 alkoxy groups, C_1 - C_4 alkylthio groups, C_1 - C_5 alkanoyloxy groups, C_2 - C_5 alkoxycarbonyl groups, halogen atoms, cyano groups, nitro groups, amino groups, monoand dialkylamino groups in which the or each alkyl part is C_1 - C_4, carbamoyl groups, monoand dialkylcarbamoyl groups in which the or each alkyl part is C_1 - C_4, and C_1 - C_5 alkanoylamino groups;

and salts thereof.

[0044] In the compounds of formula (IV), where R^{11} or R^{12} or substituent (a), (b) or (c) represents a halogen atom, this may be a fluorine, chlorine, bromine or iodine atom and is preferably a chlorine or fluorine atom.

[0045] Where R^{11}, R^{12}, R^{13}, R^{14}, R^{16}, R$^{16'}$, R^{17}, R^{19} or R^{20} or substituent (c) represents an alkyl group, this has from 1 to 4 carbon atoms and may be a straight or branched chain group. Examples of such groups include the methyl, ethyl, propyl, isopropyl, butyl, sec-butyl and t-butyl groups, of which the methyl, ethyl, propyl, isopropyl, butyl and sec-butyl groups are preferred and the methyl and ethyl groups are most preferred.

[0046] Where R^{11}, R^{12}, R^{16}, R$^{16'}$ or R^{20} represents a substituted alkyl group, the alkyl part may be any of the alkyl groups exemplified above and: in the case of R^{11} or R^{12}, the substituent is selected from substituents (a); and, in the case of R^{16}, R$^{16'}$ or R^{20}, the substituent is selected from substituents (b); the substituents being defined above and exemplified elsewhere herein.

[0047] Where R^{11}, R^{12}, R^{13} or R^{14} or substituent (a), (b) or (c) represents an alkoxy group, this has from 1 to 4 carbon atoms and may be a straight or branched chain group. Examples of such groups include the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and t-butoxy groups, especially the methoxy, ethoxy, propoxy, isopropoxy and butoxy groups.

[0048] Where R^{11} or R^{12} represents a C_2 - C_6 alkoxyalkoxy group, each of the alkoxy parts may have from 1 to 5, preferably from 1 to 4, carbon atoms, provided that the total number of carbon atoms in the two alkoxy groups does not exceed 6, and preferred examples of such alkoxy groups are as given above. Examples of the alkoxyalkoxy groups include the methoxymethoxy, ethoxymethoxy, propoxymethoxy, butoxymethoxy, 1- and 2- methoxyethoxy, 1- and 2-ethoxyethoxy, 1- and 2- butoxyethoxy and 1-, 2- and 3- methoxypropoxy groups, of which the methoxymethoxy, ethoxymethoxy, propoxymethoxy, butoxymethoxy, methoxyethoxy, ethoxyethoxy and butoxyethoxy groups are preferred.

[0049] Where R^{16} represents a C_2 - C_8 alkenyl or alkynyl group, it may be, for example, a vinyl, 1-propenyl, allyl, 1-butenyl, 2-butenyl, 3-butenyl, butadienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1,3-dimethylbutenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1,3-, 1,4-, 1,5-, 2,4-, 2,5- and 3,5-hexadienyl, 1-, 2-, 3-, 4-, 5- and 6-heptenyl, 1-, 2-, 3-, 4-, 5-, 6- and 7- octenyl, ethynyl, 1-propynyl, 1-, 2- and 3- butynyl, 1-, 2-, 3- and 4- pentynyl, 1-, 2-,

3-, 4- and 5- hexynyl, 1-, 2-, 3-, 4-, 5- and 6- heptynyl, 1-, 2-, 3-, 4-, 5-, 6- and 7- octynyl and propargyl groups, of which the 1-propenyl, allyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-dimethylbutenyl, hexadienyl and propargyl groups are preferred. Such groups may be unsubstituted or they may be substituted by at least one of substituents (b), defined above and exemplified generally herein. However, they are preferably unsubstituted.

[0050] Where R^{16}, R^{17} or substituent (b) represents a cycloalkyl group, this may contain from 3 to 8 ring atoms, and examples are the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl cycloheptyl and cyclooctyl groups, of which the cyclopentyl and cyclohexyl groups are more preferred. Such groups may be unsubstituted or they may be substituted by at least one of substituents (c), defined above and exemplified generally herein. However, they are preferably unsubstituted.

[0051] Where R^{16} represents a heterocyclic group, this may be a saturated or unsaturated group containing from 3 to 6 ring atoms, of which at least one, and preferably from 1 to 3, is a nitrogen, oxygen or sulphur atom. More preferably the group has from 0 to 3 such nitrogen atoms, 0, 1 or 2 such oxygen atoms and 0, 1 or 2 such sulphur atoms, provided that the total number of hetero-atoms is not less than 1 and does not exceed 3. Where the group is unsaturated, it may be non-aromatic or aromatic in character. The group may be monocyclic or it may be fused to one or two benzene rings to produce a bicyclic or tricyclic group, in which the heterocyclic part may be aromatic or non-aromatic in character. Examples of such groups include the oxiranyl, oxetanyl, aziridinyl, azetidinyl, thiranyl, thietanyl, furyl, thienyl, pyrrolyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, pyranyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, naphthyridynyl, xanthenyl, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, thiazolidinyl, imidazolidinyl, imidazolinyl, oxazolinyl, oxazolidinyl, pyrazolidinyl, piperazyl, tetrahydropyrimidinyl, dihydropyridazinyl, morpholinyl, thiomorpholinyl, indolinyl, tetrahydroquinolyl, pyrrolidonyl, piperidonyl, pyridonyl, thianthrenyl, chromenyl, phenoxathiinyl, 2H-pyrrolyl, isoindolyl, 3H-indolyl, indazolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, carbazolyl, phenanthridinyl, acridinyl, perimidinyl, phenazinylphenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, pyrazolinyl, indolinyl and isoindolinyl groups. Such groups may be unsubstituted or they may have at least one substituent selected from substituents (c), defined above and exemplified elsewhere herein.

[0052] Where R^{11} or R^{12} represents a group of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16'}R^{16'}$, the two groups represented by $R^{16'}$ may be the same or different and may be selected from those groups represented by R^{16} and defined and exemplified above. Alternatively, the two groups $R^{16'}$, together with the nitrogen atom to which they are attached, may form a nitrogen-containing heterocyclic group, which may optionally have an additional nitrogen, oxygen or sulphur hetero-atom; such a group may contain from 3 to 7 atoms in total (i.e. including the aforementioned nitrogen atom) and may be saturated or unsaturated. If it is unsaturated the unsaturation may be aromatic or non-aromatic in character, provided that the group has a nitrogen atom which can provide the nitrogen atom of the group $-NR^{16'}R^{16'}$. Examples of such groups include the aziridinyl, azetidinyl, pyrrolyl, imidazolyl, pyrazolyl, pyrrolidinyl, thiazolidinyl, imidazolidinyl, imidazolinyl, oxazolinyl, oxazolidinyl, pyrazolidinyl, piperazyl, tetrahydropyrimidinyl, dihydropyridazinyl, pyrrolidonyl, piperidonyl, pyridonyl, pyrazolinyl, azepinyl, perhydroazepinyl, oxazepinyl and thiazepinyl groups. Such groups may be unsubstituted or they may have at least one substituent selected from substituents (c), defined above and exemplified elsewhere herein.

[0053] Where R^{11} or R^{12} represents a group of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16''}NR^{16''}R^{16''}$, the group $-NR^{16''}R^{16''}$ may be a group of formula $-NR^{16}R^{16}$, in which each R^{16} is as defined above, or it may be a group of formula $-NR^{16'}R^{16'}$, which forms a heterocyclic group as exemplified in the preceding paragraph. Alternatively, two of the symbols $R^{16''}$ attached to different nitrogen atoms may form a heterocyclic ring containing at least two nitrogen atoms and optionally another hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms. Examples of such groups include the divalent groups derived by removal of a hydrogen atom from each of the two adjacent nitrogen atoms of the ring systems: diaziridine, diazete, diazetidine, pyrazolidine, pyrazoline, 1,2-dihydropyridazine, 1,2,3,4-tetrahydropyridazine, 1,2,5,6-tetrahydropyridazine, perhydropyridazine, 1,2-dihydro-1,2- diazepine and perhydro-1,2-diazepine.

[0054] Where substituent (a) or (c) represents an alkanoyloxy group, it contains from 1 to 5 carbon atoms and may be a straight or branched chain group. Examples of such groups include the formyloxy, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy and pivaloyloxy groups. Such groups may be substituted or unsubstituted.

[0055] Where substituent (a), (b) or (c) is an alkylthio group, this contains from 1 to 4 carbon atoms and may be a straight or branched chain group. Examples of such groups include the methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio and t-butylthio groups.

[0056] Where substituent (b) or (c) is an alkoxycarbonyl group, this has a total of from 2 to 5 carbon atoms, i.e. the alkoxy part has from 1 to 4 carbon atoms, and this alkoxy part may be any of those alkoxy groups exemplified above. Examples of such alkoxycarbonyl groups include the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, sec-butoxycarbonyl and t-butoxycarbonyl groups.

[0057] Where substituent (b) is a cyanoalkylthio group, this may be a straight or branched chain group having from 2 to 5 carbon atoms in total, i.e. the alkyl part has from 1 to 4 carbon atoms and may be any of those alkyl groups exemplified above. Examples of such cyanoalkylthio groups include the cyanomethylthio, 1-cyanoethylthio, 2-cya-

noethylthio, 1-cyanopropylthio, 2-cyanopropylthio, 3-cyanopropylthio, 1-cyanobutylthio, 2-cyanobutylthio, 3-cyanobutylthio, 4-cyanobutylthio, 3-cyano-2-methylpropylthio, 2-cyano-2-methylpropylthio and 2-cyano-1-methylethylthio groups.

[0058] Where substituent (b) is an aryl group, this has from 6 to 14 ring carbon atoms and is a carbocyclic group. Examples of such groups include the phenyl, naphthyl (1- or 2-) and anthryl groups, of which the phenyl and naphthyl groups are preferred and the phenyl group is most preferred.

[0059] Where substituent (b) is an aromatic heterocyclic group, this has from 5 to 8 ring atoms of which from 1 to 4 are hetero-atoms selected from nitrogen, oxygen and sulphur hetero-atoms and which has at least two conjugated double bonds to give an aromatic character to the ring. More preferably the group has from 0 to 4 such nitrogen atoms, 0, 1 or 2 such oxygen atoms and 0, 1 or 2 such sulphur atoms, provided that the total number of hetero-atoms is not less than 1 and does not exceed 4. The group may be monocyclic or it may be fused to a benzene ring to form a bicyclic ring system. Such groups may be substituted or unsubstituted and, if substituted, have at least one substituent selected from substituents (c), defined above and exemplified elsewhere herein. Examples of such aromatic heterocyclic groups include the pyridyl, thienyl, furyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, indolyl, benzofuryl, isobenzofuryl, chromenyl, 2H-pyrrolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl and cinnolinyl groups.

[0060] Where substituent (b) is an aryloxy or arylthio group, the aryl part has from 6 to 10 carbon atoms and is a carbocyclic aryl group. Examples include the phenoxy, phenylthio, 1-naphthyloxy, 2-naphthyloxy, 1-naphthylthio and 2-naphthylthio groups, of which the phenoxy and phenylthio groups are preferred. Such groups may be substituted or unsubstituted and, if substituted, the substituent is selected from substituents (c), defined above and exemplified elsewhere herein.

[0061] Where substituent (c) is a mono- or dialkylamino group, the or each alkyl group may have from 1 to 4 carbon atoms and may be a straight or branched chain group. Examples of alkyl groups are given above. Examples of such monoand dialkylamino groups include the methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino and N-ethyl-N-butylamino groups.

[0062] Where substituent (c) is a mono- or dialkylcarbamoyl group, the or each alkyl group may have from 1 to 4 carbon atoms and may be a straight or branched chain group. Examples of alkyl groups are given above. Examples of such mono- and dialkylcarbamoyl groups include the methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, N-methyl-N-propylcarbamoyl and N-ethyl-N-butylcarbamoyl groups.

[0063] Where substituent (c) is a C_1 - C_5 alkanoylamino group, the alkanoyl part may be a straight or branched chain group and examples include the formylamino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, isovalerylamino and pivaloylamino groups.

[0064] Where R^{17} represents an aralkyl group, the alkyl part has from 1 to 4 carbon atoms and may be any of the alkyl groups exemplifed above. The aryl part has from 6 to 10 carbon atoms in its ring and again, may be any of the aryl groups exemplified above. Examples of such aralkyl groups include the benzyl, phenethyl, a-methylbenzyl, 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl and 4-phenylbutyl groups, of which the benzyl and phenethyl groups are preferred.

[0065] In general, in the discussion above, where reference is made to a substituted group, there is no particular restriction on the number of substituents, except such as may be imposed by the number of substitutable positions, or possibly by steric constraints, each of which is well recognised by those skilled in the art. However, as a general rule, we normally find it convenient to have no more than 3 such substituents, and sometimes fewer, i.e. 1, 2 or 3. More preferably, the number of the substituents is 1, 2 or 3 where the substituent is a halogen atom, and 1 in other cases.

[0066] It will also be appreciated that the compounds of formula (IV) may be further derivatised at the 5-position, for example, to provide an ester or salt thereof. The 15-hydroxyl group may also be converted to a hydroxyimino group, if desired.

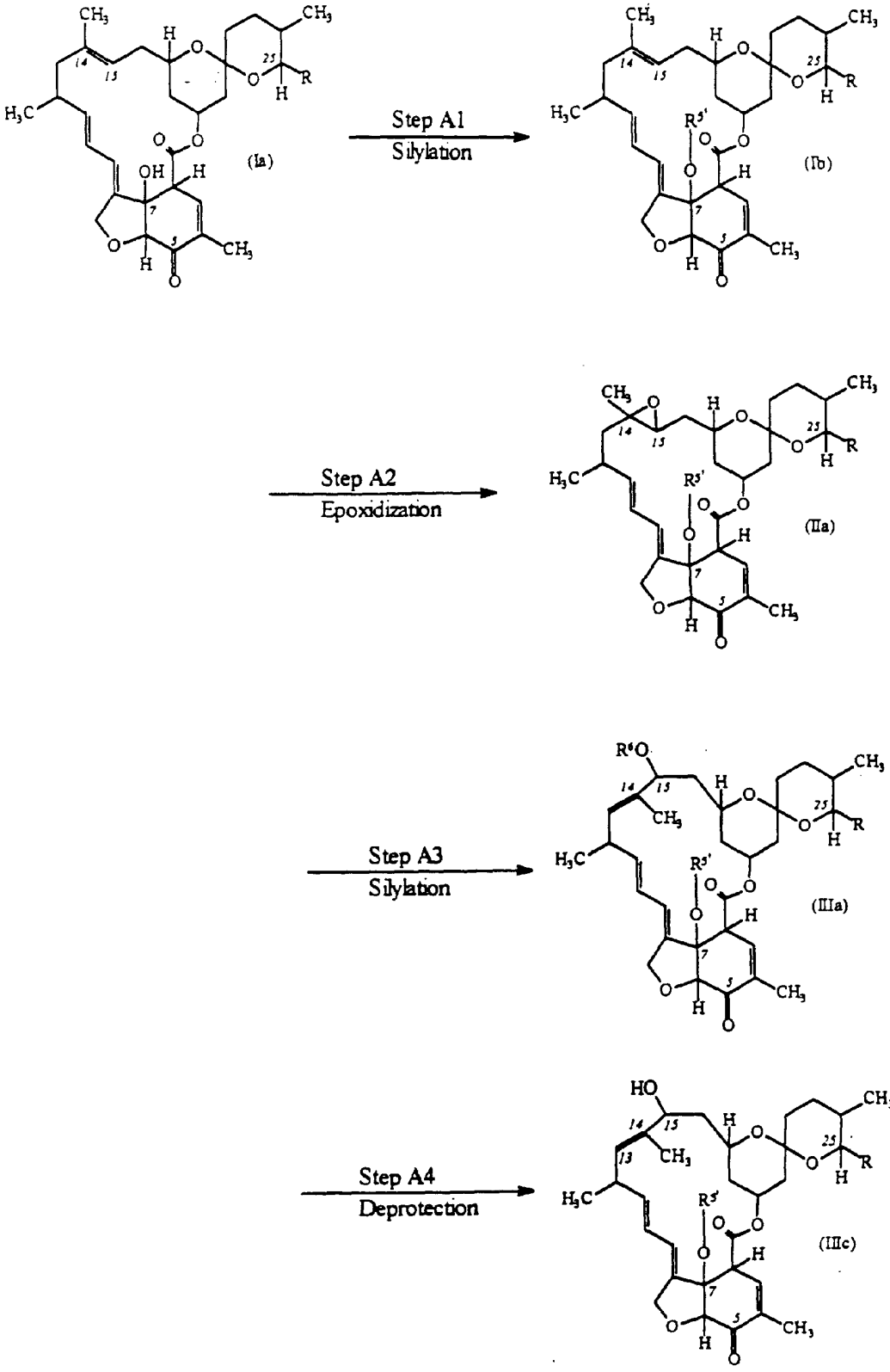
[0067] In the processes of the invention, the most preferred end-products are derivatives of milbemycins A_4 and A_3, the most preferred compounds being 13-{2-[4-(N-methanesulphonyl-N-methylamino)phenyl]- ethoxy}milbemycin A_4 and 13-{2-[4-(N-methanesulphonyl-N-methylamino)phenyl]- ethoxy}milbemycin A_3.

[0068] In practice, it will often be the case that the compound of formula (I) used as the starting material will comprise a mixture of A_4 and A_3 milbemycin derivatives (wherein R is an ethyl or a methyl group).

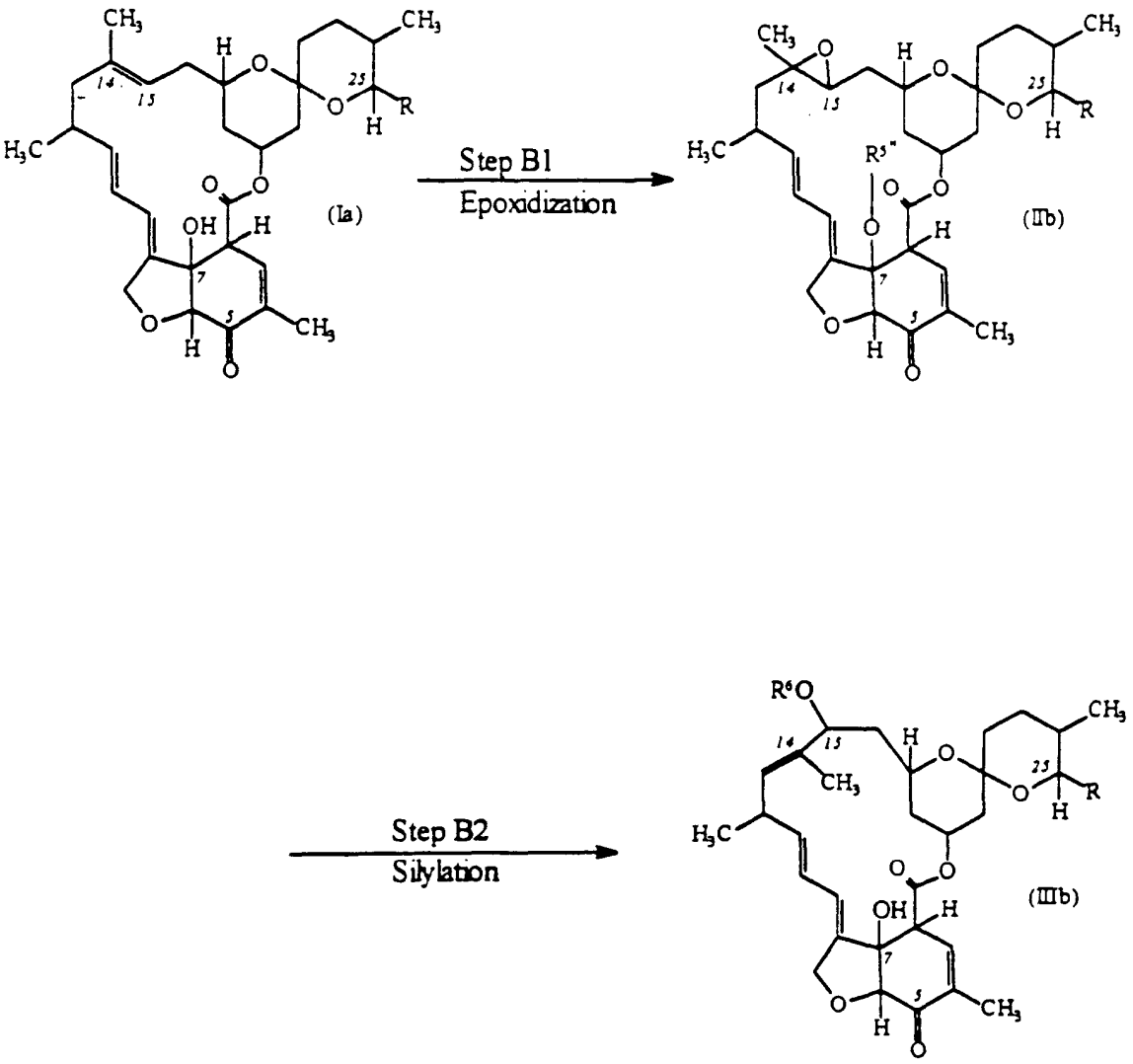
[0069] The following two reaction schemes, A and B, show two processes of the present invention for obtaining a compound of formula (IV) from a compound of formula (I) wherein R^5 represents a hydrogen atom. In the following reaction scheme A, the hydroxy group at position 7 is protected prior to 14,15-epoxidisation. In reaction scheme B, 14,15-epoxidisation is carried out without first protecting the hydroxy group at the 7 position.

[0070] It will be appreciated that reaction scheme A involves the compounds of formulae (I), (II) and (III) of the present invention, while reaction scheme B proceeds from a compound of formula (I) wherein R^5 represents a hydrogen atom directly to a compound of formula (IIb), without the necessity of first protecting the 7-hydroxyl group.

REACTION SCHEME A



REACTION SCHEME B



[0071] In the above formulae, R and R^6 are as defined above, $R^{5'}$ represents a hydroxy-protecting group of formula -SiR2R3R4, as defined above, and $R^{5''}$ represents a hydrogen atom.

Reaction Scheme A

[0072] In step A1, a compound of general formula (Ib) is prepared by reacting, in solution, a compound of formula (Ia) with a silylating reagent in the presence of an acid binding agent. This step is optional.

[0073] Any acid binding agents suitable for use in the silylation reaction, as are well known in the art, may be employed in step A1, without any particular restrictions. Acid binding agents frequently used for silylation include imidazole, 4-dimethylaminopyridine and triethylamine, any of which may be employed in step A1. We prefer that the acid binding agent is an organic base, such as imidazole or triethylamine, and we most prefer imidazole as the acid binding agent.

[0074] The amount of acid binding agent to be used in step A1 will be readily apparent to those skilled in the art, and will mainly be determined by the amount of silylating agent employed. However, suitable amounts of acid binding agent are generally in the region of about 1 to about 2 molar equivalents, preferably about 1 molar equivalent, by reference to the silylating agent.

[0075] Any suitable silylating agent may be employed, but we prefer to use a tri-substituted silylating agent of the formula X-$R^{5'}$ (wherein X represents a halogen atom, such as chlorine, bromine or iodide, but preferably chlorine; and

$R^{5'}$ is as defined above). Trimethylsilyl chloride, and t-butyldimethylsilyl chloride are preferred tri-substituted silylating agents of formula X-$R^{5'}$, and trimethylsilyl chloride is the most preferred silylating agent.

[0076] The amount of silylating agent to be used will be readily apparent to those skilled in the art, but will generally be in the range of from about 1 to about 10 molar equivalents, more preferably in the range of from about 1 to about 5 molar equivalents, of the compound of formula (Ia).

[0077] There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents include: aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, 1,2-dichloroethane and chloroform; esters, such as ethyl acetate and propyl acetate; amides, such as dimethylformamide and dimethylacetamide; sulphoxides, such as dimethyl sulphoxide; and nitriles, such as acetonitrile and propionitrile. The most preferred solvents are toluene and methylene chloride.

[0078] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to perform the reaction at a temperature between about -30 and about 100°C, preferably between about -20 and about 0°C. The time allowed for the reaction is not critical to the present invention, and will generally depend on such factors as temperature, solvent and the nature of the reagents employed. In general, we find it convenient to carry out the reaction for a period of between about 1 and about 5 hours, preferably between about 1 and about 2 hours.

[0079] After completion of the reaction, the reaction product can be recovered easily from the reaction mixture by conventional procedures, such as by washing the reaction mixture with water, and then evaporating the washed reaction mixture to dryness under reduced pressure. The product obtained by this procedure can then be used in step A2 without further purification. However, if desired, the product can be further purified by, for example, recrystallisation or a chromatographic technique, such as column chromatography, particularly silica gel column chromatography.

[0080] In step A2, a compound of formula (IIa) is prepared by oxidising a compound of formula (Ib), in solution, with a reagent system comprising effective amounts of Oxone and one or more ketones to provide the necessary peroxide, and details are given in the description of step B1 below.

[0081] After completion of the epoxidisation reaction, the desired product can be recovered easily from the reaction mixture by conventional procedures. For example, an aqueous solution of sodium thiosulphate can be added to the reaction mixture to decompose excess peroxy acid, followed by washing the reaction mixture with an aqueous solution of sodium hydrogencarbonate and water, in that order, and then evaporating the solvent under reduced pressure. The product obtained by this procedure can then be used in step A3 without further purification. However, if desired, the product can be further purified by, for example, recrystallisation or a chromatographic technique, such as column chromatography, particularly silica gel column chromatography.

[0082] In step A3, a compound of formula (IIIa) is prepared by reacting a compound of formula (IIa), in solution, with a silylating agent in the presence of a base.

[0083] Any suitable silylating agent may be employed in this step, and appropriate silylating agents will be readily apparent to those skilled in the art. We find it convenient to use tri-substituted silyl triflates having the formula $CF_3SO_2OSiR^7R^8R^9$ (wherein R^7, R^8 and R^9 are as defined above), such as trimethyl triflate, phenyldimethyl triflate and t-butyldimethyl triflate, preferably t-butyldimethyl triflate. Where any of R^7, R^8 and R^9 is a phenyl group or a benzyl group, and especially where the resulting tri-substituted silyl group is not commercially available, then triflates containing these groups can be prepared in accordance with the method described in Tetrahedron Letters (1981), 22, 3455.

[0084] The amount of silylating agent used will be readily apparent to those skilled in the art, but will generally be in the range of from about 1.0 to about 10 molar equivalents, more preferably in the range of from about 1.5 to about 3.0 molar equivalents, of the compound of formula (IIa).

[0085] Any suitable base may be used in this step, and appropriate bases will be readily apparent to those skilled in the art. In general, there is no particular restriction on the base, provided that it does not have an unduly adverse effect on the reaction. We find it convenient to use a base selected from 2,6-lutidine, pyridine, 2,6-di-t-butylpyridine and triethylamine, and we prefer to use 2,6-lutidine.

[0086] The amount of base to be used will be readily apparent to those skilled in the art, and will mainly be determined by the amount of silylating agent employed. However, suitable amounts of base are generally in the region of from about 1 to about 10 molar equivalents, preferably from about 2 to about 5 molar equivalent, by reference to the silylating agent.

[0087] There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents include: aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, 1,2-dichloroethane and chloroform; esters, such as ethyl acetate and propyl acetate; amides, such as dimethylformamide and dimethylacetamide; sulphoxides, such as dimethyl sulphoxide; and nitriles, such as acetonitrile and propionitrile. The most preferred solvents are the aromatic hydrocarbons and halogenated hydrocarbons, particularly toluene and methylene chloride.

[0088] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to perform the reaction at a temperature between about -50 and about 100°C, preferably between about -30 and about 50°C. The time allowed for the reaction is not critical to the present invention, and will generally depend on such factors as temperature, solvent and the nature of the reagents employed. In general, we find it convenient to carry out the reaction for a period of between about 7 and about 48 hours, preferably between about 12 and about 24 hours.

[0089] After completion of the reaction, the reaction product can be recovered easily from the reaction mixture by conventional procedures. For example, the reaction mixture can be washed with 1 M aqueous hydrochloric acid, water, an aqueous solution of sodium hydrogencarbonate and water, in that order, followed by evaporation of the solvent under reduced pressure. The product obtained by this procedure can then be used directly without further purification. However, if desired, the product can be further purified by, for example, recrystallisation or a chromatographic technique, such as column chromatography, particularly silica gel column chromatography.

[0090] Step A4 is optional. In this step, a compound of formula (IIIc) is prepared by deprotecting a compound of formula (IIIa), in a solvent, in the presence of an acid.

[0091] There is no particular restriction on the acid which can be used in this step, and suitable acids will be readily apparent to those skilled in the art. Examples of acids which can be used in this step include: mineral acids, such as hydrochloric acid, hydrobromic acid and sulphuric acid, preferably hydrochloric acid; aliphatic carboxylic acids, such as formic acid and trifluoroacetic acid, preferably trifluoroacetic acid; monoalkylsulphuric acids, such as monomethylsulphuric acid and monoethylsulphuric acid; sulphinic acids, such as benzenesulphinic acid; and sulphonic acids, such as methanesulphonic acid and p-toluenesulphonic acid. In general, we find it convenient to use the acid in great excess.

[0092] There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents include: aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as dichloromethane, 1,2-dichloroethane and chloroform; esters such as ethyl acetate and propyl acetate; ethers, such as diethyl ether, tetrahydrofuran, dioxane and dimethoxyethane; and nitriles such as acetonitrile. The most preferred solvents are toluene and dichloromethane.

[0093] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to perform the reaction at a temperature between about -10 and about 50°C, preferably between about 20 and about 30°C. The time allowed for the reaction is not critical to the present invention, and will generally depend on such factors as temperature, solvent and the nature of the reagents employed. In general, we find it convenient to carry out the reaction for a period of between about 30 minutes and about 5 hours, preferably between about 1 and about 2 hours.

[0094] After completion of the reaction, the reaction product can be recovered easily from the reaction mixture by conventional procedures. For example, the reaction mixture can be washed with water, an aqueous solution of sodium hydrogencarbonate and water, in that order, followed by evaporation of the solvent under reduced pressure. The product obtained by this procedure can then be used directly without further purification. However, if desired, the product can be further purified by, for example, recrystallisation or a chromatographic technique, such as column chromatography, particularly silica gel column chromatography.

Reaction Scheme B

[0095] In step B1, a compound of formula (IIb) is prepared by reacting a compound of formula (Ia) with a peroxide in the presence of a solvent.

[0096] The peroxide is provided by a mixture of Oxone (trade mark, potassium peroxymonosulphate: $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, Du Pont Japan Limited) and one or more ketones.

[0097] The amount of potassium peroxymonosulphate used is not critical to the present invention provided that, in combination with the ketone(s), sufficient peroxide is generated to enable the epoxidation reaction to proceed. In general, we find it convenient to use potassium peroxymonosulphate in an amount of from about 0.5 to about 5.0 molar equivalent, preferably from about 0.7 to about 1.5 molar equivalent of the compound of formula (Ia).

[0098] The nature of the ketones used is not critical to the present invention provided that, in combination with potassium peroxymonosulphate, sufficient peroxide is generated to enable the epoxidation reaction to proceed. Suitable ketones include acetone, methyl ethyl ketone, cyclohexanone, trifluoroacetone and chloroacetone, preferably acetone.

[0099] The ketone(s) will generally be used in great excess so that, in effect, they can also act as the solvent. However, where other solvents are used, there is no particular restriction on the nature of the solvent, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents include: a mixture of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, trifluoroacetone and chloroacetone together with one or more aromatic hydrocarbons or halogenated hydrocarbons as described above with respect to step A1. We prefer that the solvent is either a mixture of acetone and benzene, acetone and toluene,

acetone and methylene chloride or acetone and 1,2-dichloroethane, we most prefer that the solvent is a mixture of acetone and methylene chloride.

[0100] Where a mixed solvent is employed, then a suitable ratio of components (v/v) is in the region of about 0.5 : 2, and is preferably in the region of about 0.9 : 1.2.

[0101] We prefer to carry out the reaction in a bi-phasic reaction mixture, using a mixed solvent as defined above together with a phosphate buffer (pH 7.0 to 8.0).

[0102] The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to perform the reaction at a temperature between about -10 and about 100°C, preferably between about 0 and about 50°C. The time allowed for the reaction is not critical to the present invention, and will generally depend on such factors as temperature, solvent and the nature of the reagents employed. In general, we find it convenient to carry out the reaction for a period of between about 10 minutes and about 5 hours, preferably between about 30 minutes and about 2 hours.

[0103] We have found that the best results are generally obtained by maintaining the reaction at a substantially constant pH of between about 7.5 and 8.0 by adding, as required, an aqueous solution of an alkali, such as potassium hydroxide or sodium hydroxide.

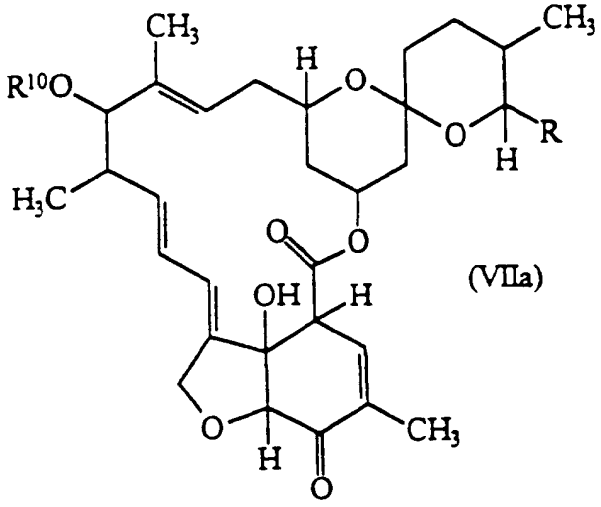
[0104] After completion of the reaction, the reaction product can be recovered easily from the reaction mixture by conventional procedures. For example, an aqueous solution of sodium thiosulphate can be added to the reaction mixture to decompose excess peroxide, followed by washing the reaction mixture with an aqueous solution of sodium hydrogencarbonate and water, in that order, and then evaporating the solvent under reduced pressure. The product obtained by this procedure can then be used in step B2 without further purification. However, if desired, the product can be further purified by, for example, recrystallisation or a chromatographic technique, such as column chromatography, particularly silica gel column chromatography.

[0105] In step B2, a compound of formula (IIIb) is prepared by reacting a compound of formula (IIb) with a silylating agent in the presence of a solvent.

[0106] In general, the reagents and conditions described above for step A3 are also appropriate to step B2. Although the reaction temperature is not critical, the preferred reaction temperature is between about -10°C and about 100°C, more preferably between about 0°C and about 5°C. The reaction product may be recovered by similar procedures to those described in relation to step A3.

[0107] A further step B3 (not shown) may be performed, if desired, to deprotect the compound of formula (IIIb) to yield a compound of formula (IIId) wherein both R^5 and $R^{6'}$ each represent a hydrogen atom. Step B3 may be performed in a similar manner as for step A4 above. However, step B3 will generally be unnecessary, as the reaction to produce a compound of formula (VIIa) can proceed when the 15- position is protected.

[0108] A compound of formula (VIIa) :



(VIIa)

(wherein R and R^{10} are as defined above) may be prepared from any of compounds of the formulae (IIIa), (IIIb) or (IIIc) in conventional fashion by reaction with an alcohol of formula $R^{10}OH$ in the presence of an acid.

[0109] Hydrogenation of the resulting compound of formula (VIIa) by conventional procedures, such as is described in Japanese Patent Application Sho-62-70379, then yields a compound of formula (IVa).

[0110] The compound of formula (IVa) can then be used directly as an anthelmintic, for example, or can be further derivatised, such as is described in European Patent Publication No. 357 460.

[0111] The present invention is described below in more detail by way of the accompanying Examples, but it will be appreciated that the present invention is not limited thereto.

EXAMPLE 1

5-Oxo-7-deoxy-7-trimethylsilyloxymilbemycin A_4

A Compound of Formula (I)

[0112] 1.36 g of imidazole were dissolved in 30 ml of methylene chloride, and 2.41 ml of trimethylsilyl chloride was added to the resulting solution under a nitrogen stream. The resulting mixture was then cooled to -10 ± 2°C.

[0113] A solution of 2.67 g of 5-oxomilbemycin A_4 in 30 ml methylene chloride was added to the cooled mixture, and the resulting mixture was allowed to react with stirring at -10 ± 2°C for about 2 hours. After this time, the reaction mixture was washed with water and evaporated to dryness under reduced pressure to afford 2.67 g (yield 96.1%) of the title compound as an amorphous solid.

Mass spectrum (m/z):

612 (M^+ $C_{35}H_{52}O_7Si$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

3.87 (1H, singlet),
4.71 (2H, singlet),
5.01-5.05 (1H, multiplet),
6.82-6.83 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

1743, 1683.

EXAMPLE 2

5 -Oxo -7 -deoxy -7 -trimethylsilyloxy -14,15-epoxymilbemycin A_4

A Compound of Formula (IIa)

[0114] 3.06 g of 5-oxo-7-deoxy-7-trimethylsilyloxymilbemycin A_4 (prepared as described in Example 1) were dissolved in 24 ml of methylene chloride. 24 ml of a phosphate buffer (an aqueous solution of 44 mM KH_2PO_4 and 330 mM Na_2HPO_4, pH 7.5) and 24 ml of acetone were added to the resulting solution, which was then cooled to a temperature of between 0 and 5°C. After cooling, a solution of 3.04 g of potassium peroxymonosulphate (Oxone, Trade Mark of Du Pont) in 24 ml of a phosphate buffer (pH 7.5, as defined above) was added in a dropwise fashion over a period of about 30 minutes. During this time, a 3 M aqueous solution of potassium hydroxide was added, as required, in order to maintain the pH in the region of 7.5 to 8.0. The resulting mixture was allowed to react at this pH at a temperature of between 0 and 5°C for about 2 hours. After this time, 30 ml of an aqueous solution of 10% w/v sodium thiosulphate was added to the reaction mixture in order to decompose any excess peroxide, and the reaction mixture was then washed with a 5% w/v aqueous solution of sodium hydrogencarbonate and water, in that order, and subsequently evaporated to dryness under reduced pressure to afford 3.08 g (yield 98.0%) of the title compound as an amorphous solid.

Mass spectrum (m/z):

628 (M^+ $C_{35}H_{52}O_8Si$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

2.65 (1H, doublet, J=10.0 Hz),
3.75-3.85 (1H, multiplet),

3.90 (1H, singlet),
4.69-4.80 (2H, multiplet),
6.84-6.85 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

1743, 1681.

EXAMPLE 3

5 -Oxo-14,15-epoxymilbemycin A_4

A Compound of Formula (IIb)

[0115] 24 ml of a phosphate buffer (pH 7.5, as defined in Example 2 above) and 24 ml of acetone were added to a solution of 3.06 g of 5-oxomilbemycin A_4 in 24 ml of methylene chloride, and the resulting mixture was cooled to a temperature of between 0 and 5°C. A solution of 3.04 g of Oxone in 24 ml of a phosphate buffer (pH 7.5, as defined in Example 2 above) was added in a dropwise fashion over a period of about 30 minutes. During this time, a 3 M aqueous solution of potassium hydroxide was added, as required, in order to maintain the pH in the region of 7.5 to 8.0. The resulting mixture was allowed to react at this pH at a temperature of between 0 and 5°C for about 2 hours. After this time, 30 ml of an aqueous solution of 10% w/v sodium thiosulphate was added to the reaction mixture in order to decompose any excess peroxide, and the reaction mixture was then washed with a 5% w/v aqueous solution of sodium hydrogencarbonate and water, in that order, and subsequently evaporated to dryness under reduced pressure to afford 3.08 g (yield 98.0%) of the title compound as an amorphous solid.
Mass spectrum (m/z):

556 (M^+ $C_{32}H_{44}O_8$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

2.60 (1H, doublet, J=9.2 Hz),
3.07 (1H, doublet of triplets, J=2.4, 9.3 Hz),
3.53 (1H, singlet),
3.58-3.59 (1H, multiplet),
3.88 (1H, singlet),
6.62 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

3479, 1740, 1683.

EXAMPLE 4

5-Oxo-7,15-bistrimethylsilyloxy-7-deoxy-$\Delta^{13,14}$-milbemycin A_4

A Compound of Formula (IIIa)

[0116] 3.14 g of 5-oxo-7-deoxy-7-trimethylsilyloxy-14,15-epoxymilbemycin A_4 (prepared as described in Example 2) were dissolved in 35 ml of toluene. The resulting solution was cooled to a temperature of between 0 and 5° C, after which 2.02 ml of 2,6-lutidine and 1.67 ml of trimethylsilyl triflate (prepared as described in Preparation 1) were added. The resulting mixture was then stirred at a temperature of between 0 and 5°C for 6 to 7 hours in a nitrogen stream. After this time, the mixture was left to stand overnight at a temperature of between 0 and 5°C. Subsequently, the reaction mixture was washed with: 1 M hydrochloric acid; water; a 5% w/v aqueous solution of sodium hydrogencarbonate; and water, in that order. The washed reaction mixture was then evaporated to dryness under reduced pressure to afford 3.02 g (yield 89.2%) of the title compound as an amorphous solid. The powder thus obtained was further purified by silica gel column chromatography (using methylene chloride as eluent) to afford 2.87 g (yield 82%) of the title compound as an amorphous solid.
Mass spectrum (m/z) :

700 (M^+ $C_{38}H_{60}O_8Si_2$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δppm:

3.94 (1H, singlet),
3.94-3.99 (1H, multiplet),
5.04 (1H, doublet, J=9.3 Hz),
6.74-6.75 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

1746, 1684.

EXAMPLE 5

5-Oxo-7-deoxy-7-trimethylsilyloxy-15-phenyldimethylsilyloxy-$\Delta^{13,14}$-milbemycin A_4

A Compound of Formula (IIIa)

[0117] 2.0 g of 5-oxo-7-deoxy-7-trimethylsilyloxy-14,15-epoxymilbemycin A_4 (prepared as described in Example 2) were dissolved in 50 ml of toluene, and the resulting solution was cooled to a temperature of between 0 and 5°C under a nitrogen stream. 1.34 ml of phenyldimethylsilyl triflate (prepared as described in Preparation 1) and 1.5 ml of 2,6-lutidine were added to the cooled solution, and the reaction was allowed to proceed overnight at a temperature of between 0 and 5°C. The reaction mixture was then washed with: 1M aqueous hydrochloric acid; water; a 5% w/v aqueous solution of sodium hydrogencarbonate; and water, in that order, and was then evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (using methylene chloride as the eluent) to afford 3.4 g (yield 70%) of the title compound as an amorphous solid.
Mass spectrum (m/z):

762 (M^+ $C_{43}H_{62}O_8Si_2$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

3.42 (1H, triplet, J=2.4 Hz),
3.93 (1H, singlet),
3.90-3.95 (1H, multiplet),
6.72-6.74 (1H, multiplet),
7.62-7.63 (5H, multiplet).

Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1}:

1730, 1670.

EXAMPLE 6

5 -Oxo-15-t-butyldimethylsilyloxy-$\Delta^{13,14}$-milbemycin A_4

A Compound of Formula (IIIb)

[0118] 5.0 g of 5-oxo-14,15-epoxymilbemycin A_4 (prepared as described in Example 3) were dissolved in 25 ml of toluene, and the solution was cooled to a temperature of between 0 and 5°C. 2.02 ml of 2,6-lutidine, 10.5 ml of triethylamine and 4.05 ml of t-butyldimethylsilyl triflate were added to the cooled solution, which was then stirred at a temperature of between 0 and 5°C for 6 to 7 hours under a nitrogen stream, after which time the mixture was left to stand overnight at a temperature of between 0 and 5°C. After this time, the reaction mixture was washed with 1M aqueous hydrochloric acid, water, a 5% w/v aqueous solution of sodium hydrogencarbonate, and water, in that order, followed by evaporation to dryness under reduced pressure to afford 3.02 g (yield 89.2%) of the target compound. The powder thus obtained was purified by silica gel column chromatography (using methylene chloride as the eluent) to afford 5.12 g (yield 85%) of the title compound as an amorphous solid.

Mass spectrum (m/z) :

670 (M^+ $C_{38}H_{59}O_8Si$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

2.97 (1H, doublet of triplets, J=1.9, 9.6 Hz),
3.52-3.54 (1H, multiplet),
3.93 (1H, singlet),
3.96 (1H, doublet of doublets, J=6.0, 9.5 Hz),
6.54-6.55 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

3486, 1716, 1689.

EXAMPLE 7

5-Oxo-15-trimethylsilyloxy-$\Delta^{13,14}$-milbemycin A_4

A Compound of Formula (IIIb)

[0119] 10.0 g of 5-oxo-14,15-epoxymilbemycin A_4 (prepared as described in Example 3) were dissolved in 100 ml of toluene, and the solution was cooled to a temperature of between 10 and 15°C. 6.2 ml of 2,6-lutidine and 6.5 mg of trimethylsilyl triflate were added to the cooled solution, which was then stirred for an hour under a nitrogen stream to effect the reaction. After this time, the reaction mixture was washed with 1M aqueous hydrochloric acid, water, a 5% w/v aqueous solution of sodium hydrogencarbonate, and water, in that order, and was then evaporated to dryness under reduced pressure to afford 10.13 g (yield 90.0%) of the target compound. The powder thus obtained was purified by silica gel column chromatography (using methylene chloride as the eluent) to afford 9.46 g (yield 84%) of the title compound as an amorphous solid.
Mass spectrum (m/z) :

628 (M^+ $C_{35}H_{52}O_8Si$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

2.97 (1H, doublet of triplets, J=2.1, 9.6 Hz),
3.52-3.54 (1H, multiplet),
3.80-3.90 (1H, multiplet),
3.93 (1H, singlet),
3.96 (1H, doublet of doublets, J=6.0, 9.5 Hz),
6.54-6.55 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

3500, 1720, 1675.

EXAMPLE 8

5-Oxo-7-deoxy-7-trimethylsilyloxy-15-hydroxy-$\Delta^{13,14}$-milbemycin A_4

A Compound of Formula (IIIc)

[0120] 3.0 g of 5-oxo-7,15-bistrimethylsilyloxy-7-deoxy $\Delta^{13,14}$-milbemycin A_4 was dissolved in 20 ml of ethyl acetate, and 20 ml of 1 M aqueous hydrochloric acid was added to the resulting solution at a temperature of between 20 and 25°C, followed by stirring for 1.5 hours. After this time, the reaction mixture was washed with water, a 5% w/v aqueous solution of sodium hydrogencarbonate and water, in that order, and was then evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (using ethyl acetate/n-hexane in a ratio of

1/1.2 by volume as the eluent) to afford 1.41 g (yield 52.4 %) of the title compound as an amorphous solid.
Mass spectrum (m/z) :

628 (M^+ $C_{35}H_{52}O_8Si$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

3.94 (1H, singlet),
4.08 (1H, doublet of doublets, J=3.9 Hz, 10.7 Hz),
5.16 (1H, doublet, J=10.7Hz),
6.74-6.76 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

3513, 1745, 1681.

EXAMPLE 9

5-Oxo-13-{2-[4-(N-methanesulfonyl-N-methylamino)phenyl]ethoxy}milbemycin A_4

A Compound of Formula (VII)

[0121] 1. 3.02 g of 5-oxo-7,15-bistrimethylsilyloxy-7-deoxy-$\Delta^{13,14}$-milbemycin A_4 (prepared as described in Example 4) and 1.96 g of 2-{4-(N-methanesulphonyl-N-methylamino)phenyl}ethyl alcohol were dissolved in 60 ml of methylene chloride, and the resulting solution was cooled to about 15°C. 0.19 ml of trifluoromethanesulphonic acid was added to the cooled solution, which was then stirred at a temperature of between 18 and 20°C for about 1 hour under a nitrogen stream. The reaction mixture was washed with a 5% w/v aqueous solution of sodium chloride, a 5% w/v aqueous solution of sodium hydrogencarbonate, and water, in that order, and was then evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (using ethyl acetate/n-hexane in a ratio of 1 : 1.5 by volume as the eluent) to afford 2.98 g (yield 90%) of the title compound as an amorphous solid.
Mass spectrum (m/z) :

767 (M^+ $C_{42}H_{57}O_{10}NS$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

1.89 (3H, multiplet),
2.82 (3H, singlet),
3.22 (1H, doublet, J=9.8 Hz),
3.30 (3H, singlet),
3.85 (1H, singlet),
6.55 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

3475, 1737, 1682.

[0122] 2. 2.34 g of 5-oxo-7,15-bistrimethylsilyloxy-7-deoxy-$\Delta^{13,14}$-milbemycin A_4 (prepared as described in Example 4) and 1.51 g of 2-{4-(N-methanesulphonyl-N-methylamino)phenyl}ethyl alcohol were dissolved in 31 ml of methylene chloride. 0.49 g of methanesulphonic acid was added to the resulting solution, and the mixture stirred under reflux at about 40°C for between 1 and 1.5 hours under a nitrogen stream. The reaction mixture was then washed with a 5% w/v aqueous solution of sodium chloride, a 5% w/v aqueous solution of sodium hydrogencarbonate and water, in that order, followed by evaporation to dryness under reduced pressure. The residue was purified by silica gel column chromatography (using ethyl acetate/n-hexane in a ratio of 1 : 1.5 by volume as the eluent) to afford 2.33 g (yield 91%) of the title compound as an amorphous solid.

EXAMPLE 10

5-Oxo-13-{2-[4-(N-methanesulfonyl-N-methylamino)phenyl]ethoxy}milbemycin A_4

A Compound of Formula (VII)

[0123] 5.00 g of 5-oxo-15-t-butyldimethylsilyloxy$\Delta^{13,14}$-milbemycin A_4 (prepared as described in Example 6) and 3.39 g of 2-[4-(N-methanesulphonyl-N-methylamino)phenyl]ethyl alcohol were dissolved in 100 ml of methylene chloride, and the resulting solution was cooled to about 15°C. 1.36 ml of trifluoromethanesulphonic acid were added to the cooled solution, which was then stirred at a temperature of between 18 and 20°C for about 1 hour under a nitrogen stream. After this time, the reaction mixture was washed with a 5% w/v aqueous solution of sodium chloride, a 5% w/v aqueous solution of sodium hydrogencarbonate and water, in that order, followed by evaporation to dryness under reduced pressure. The residue was purified by silica gel column chromatography (using ethyl acetate/n-hexane in a ratio of 1 : 1.5 by volume as the eluent) to afford 2.98 g (yield 90%) of the title compound as an amorphous solid.
Mass spectrum (m/z) :

767 (M^+ $C_{42}H_{57}O_{10}NS$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

1.89 (3H, multiplet),
2.82 (3H, singlet),
3.22 (1H, doublet, J=9.8 Hz),
3.30 (3H, singlet),
3.85 (1H, singlet),
6.55 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

3475, 1737, 1682.

EXAMPLE 11

13-{2-[4-(N-Methanesulfonyl-N-methylamino)phenyl]ethoxy}milbemycin A_4

A Compound of Formula (IV)

[0124] 0.344 g of 5-oxo-13-{2-[4-(N-methanesulphonyl-N-methylamino)phenyl]ethoxy}milbemycin A_4 (prepared as described in either of Examples 9 and 10) was dissolved in 7.4 ml of methanol and 3.7 ml of tetrahydrofuran. The resulting solution was cooled to between -40 and -50°C, when 0.019 g of sodium borohydride and a catalytic amount of boron trifluoride diethyl etherate were added, after which the mixture was stirred for one hour. After this time, 50 ml of ethyl acetate were added to the reaction mixture, which was then washed twice with water, dried over anhydrous sodium sulphate and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (ODS, 85% aqueous acetonitrile used as eluent), and then recrystallised from ethyl acetate/hexane (in a ratio of 1 : 4 v/v) to afford 0.307 g (yield 90.0%) of the title compound as an amorphous solid.
Mass spectrum (m/z) :

769 (M^+, $C_{42}H_{59}NO_{10}S$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

1.87 (3H, singlet),
2.82 (3H, singlet),
3.21 (1H, doublet, J=7.6 Hz),
3.30 (3H, singlet),
3.95 (1H, doublet, J=6.3 Hz).

EXAMPLE 12

13-{2-[4-(N-Methanesulfonyl-N-methylamino)phenyl]ethoxy}milbemycin A_3

A Compound of Formula (IV)

a) 5-Oxo-14,15-epoxymilbemycin A_3

[0125] Following a procedure similar to that of Example 3, but using 3.0 g (5.55 mmol) of 5-oxomilbemycin A_3 as the starting material, the title compound was obtained in an amount of 2.9 g (yield 95%, 5.27 mmol) as an amorphous solid.
Mass spectrum (m/z) :

542 (M^+ $C_{31}H_{42}O_8$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

2.60 (1H, doublet, J=9.2 Hz),
3.53 (1H, singlet),
3.58-3.59 (1H, multiplet),
3.88 (1H, singlet),
6.62 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

3480, 1740, 1685.

b) 5-Oxo-15-t-butyldimethylsilyloxy-$\Delta^{13,14}$- milbemycin A_3

[0126] Following a procedure similar to that of Example 6, but using 2.0 g (3.59 mmol) of 5-oxo-14,15-epoxymilbemycin A_3 (prepared as described in a above), the title compound was afforded in an amount of 1.9 g (yield 80%, 2.87 mmol) as an amorphous solid.
Mass spectrum (m/z) :

656 (M^+ $C_{37}H_{57}O_8Si$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

3.52-3.54 (1H, multiplet),
3.93 (1H, singlet),
3.96 (1H, doublet of doublets, J=6.0, 9.5 Hz),
6.54-6.55 (1H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1}:

3486, 1720, 1690.

c) 5-Oxo-13-{2-[4-(N-methanesulphonyl-N-methylamino)phenyl]ethoxy}milbemycin A_3

[0127] 11.0 g of 2-{4-(N-methanesulphonyl-N-methylamino)phenyl}ethyl alcohol were dissolved in 100 ml of methylene chloride, and 1.40 ml of trifluoromethanesulphonic acid were added to the resulting solution, which was then stirred at room temperature for 5 minutes. 5.81 g of 5-oxo-15-t-butyldimethylsilyloxy-$\Delta^{13,14}$-milbemycin A_3 (prepared as descibed in b above) was added to the resulting mixture, which was then stirred at room temperature for 30 minutes. After this time, 500 ml of ethyl acetate were added to the reaction mixture, which was then washed with water, a 4% w/v aqueous solution of sodium hydrogencarbonate and water, in that order, dried over anhydrous sodium sulphate and subsequently evaporated to dryness under reduced pressure. The residue was recrystallised from a mixture of ethyl acetate/ cyclohexane (in a ratio of 1 : 4 v/v) and the precipitated crystals were removed by filtration. The filtrate was purified by silica gel column chromatography (using ethyl acetate/ hexane in a ratio of 3 : 7 by volume) to afford 7.42 g of the target compound (yield 91.9%).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

1.89 (3H, multiplet),
2.82 (3H, singlet),
3.23 (1H, doublet, J=9.8 Hz),
3.30 (3H, singlet),
3.86 (1H, singlet),
6.55 (1H, multiplet).

d) 13-{2-[4-(N-methanesulphonyl-N-methylamino)phenyl]ethoxy}milbemycin A_3

[0128] All of the compound obtained in c) above was dissolved in a mixture of 80 ml of methanol and 40 ml of tetrahydrofuran. The resulting solution was cooled to between -40 and -50°C, when 0.36 g of sodium borohydride and a catalytic amount of boron trifluoride diethyl etherate were added, after which the mixture was stirred for 3.5 hours. After this time, 500 ml of ethyl acetate were added to the reaction mixture, which was then washed twice with water, dried over anhydrous sodium sulphate and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (ODS, eluted with 85% v/v aqueous acetonitrile) to afford 6.74 g (yield 90.6%) of the title compound as an amorphous solid.
Mass spectrum (m/z) :

755 (M^+, $C_{41}H_{57}NO_{10}S$).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

1.87 (3H, singlet),
2.82 (3H, singlet),
3.21 (1H, doublet, J=7.6 Hz),
3.30 (3H, singlet),
3.95 (1H, doublet, J=6.3 Hz).

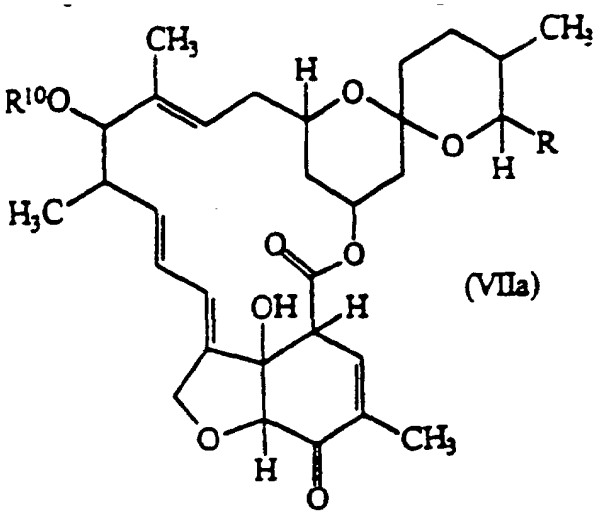
PREPARATION 1

Phenyldimethylsilyl triflate

[0129] Phenyldimethylsilyl triflate was prepared by cooling 5 ml of phenyldimethylsilyl chloride to a temperature between 0 and 5°C, and then adding 4.2 ml of trifluoromethanesulphonic acid in a dropwise fashion over a period of about 30 minutes. The resulting mixture was then stirred at a temperature of between 0 and 5°C for about 6 hours, and subsequently left to stand, with cooling, overnight. The resulting preparation could be used without any further purification.

Claims

1. A process for the preparation of a compound of formula (VIIa) :



(VIIa)

wherein R represents a methyl group, an ethyl group, an isopropyl group or a sec-butyl group, and R^{10} represents an alkyl group having from 1 to 20 carbon atoms; an alkenyl group having from 2 to 6 carbon atoms; an alkynyl group having from 2 to 6 carbon atoms; or an aralkyl group in which the alkyl part has from 1 to 10 carbon atoms and which may be unsubstituted or substituted by 1 or 2 alkoxy groups each having from 1 to 4 carbon atoms, and the aryl part has from 6 to 10 ring carbon atoms and is unsubstituted or is substituted by at least one substituent selected from:

halogen atoms; cyano groups; nitro groups; C_1 - C_4 alkyl groups; substituted C_1 - C_4 alkyl groups having at least one substituent selected from substituents (a), defined below; C_1 - C_4 alkoxy groups; C_2 - C_6 alkoxyalkoxy groups; groups of formula $-(CH_2)_nNHR^{19}$, in which: n represents 0 or the integer 1 or 2, and R^{19} represents a hydrogen atom or a C_1 - C_4 alkyl group;

groups of formula $-(CH_2)_nNR^{19}C(=O)R^{16}$,
in which:

n and R^{19} are as defined above, and

R^{16} represents: a hydrogen atom; a C_1 - C_4 alkyl group; a substituted C_1 - C_4 alkyl group having at least one substituent selected from substituents (b), defined below; a C_2 - C_8 aliphatic hydrocarbon group having one or two ethylenically unsaturated carbon-carbon double bonds, the group being unsubstituted or having at least one substituent selected from substituents (b), defined below; a C_2 - C_8 alkynyl group; a substituted C_2 - C_8 alkynyl group having at least one substituent selected from substituents (b), defined below; a C_3 - C_8 cycloalkyl group; a substituted C_3 - C_8 cycloalkyl group having at least one substituent selected from substituents (c), defined below; a carbocyclic aryl group having from 6 to 14 ring carbon atoms and being unsubstituted or having at least one substituent selected from substituents (c), defined below; or a heterocyclic group having from 3 to 6 ring atoms of which at least one is a hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms, the heterocyclic group being monocyclic or fused to one or two benzene rings and being unsubstituted or having at least one substituent selected from substituents (c), defined below;

groups of formula $-(CH_2)_nNR^{19}COCOR^{16}$
in which n, R^{16} and R^{19} are as defined above;

groups of formula $-(CH_2)_nR^{19}COCOOR^{17}$
in which n and R^{19} are as defined above and R^{17} represents a C_1 - C_4 alkyl group, a C_3 - C_8 cycloalkyl group or an aralkyl group having from 1 to 4 carbon atoms in the alkyl part and from 6 to 10 ring atoms in the aryl part, which is a carbocyclic aryl group which is unsubstituted or has at least one substituent selected from substituents (c), defined below;

groups of formula $-(CH_2)_nNR^{19}CHR^{16}NHCOR^{16}$
in which n, R^{16} and R^{19} are as defined above;

groups of formula $-(CH_2)_nNR^{19}CHR^{16}NHCONHR^{16}$
in which n, R^{16} and R^{19} are as defined above;

groups of formula $-(CH_2)_nNR^{19}CHR^{16}NHCOOR^{17}$
in which n, R^{16}, R^{17} and R^{19} are as defined above;

groups of formula $-(CH_2)_nNR^{19}C(=Y)YR^{16}$
in which n, R^{16} and R^{19} are as defined above and the two symbols Y are independently selected from oxygen and sulphur atoms;

groups of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16'}R^{16'}$
in which n, Y and R^{19} are as defined above, and the two symbols $R^{16'}$ are independently selected from R^{16}, or the two, together with the nitrogen atom to which they are attached, form a heterocyclic group having from 3 to 7 ring atoms of which one is the nitrogen atom and 0 or 1 is an additional hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms;

groups of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16''}-NR^{16''}R^{16''}$
in which n, Y and R^{19} are as defined above, and each of the symbols $R^{16''}$ is independently selected from R^{16}, or any two of the symbols $R^{16''}$, together with the nitrogen atom to which each is attached, forms a heterocyclic group having from 3 to 7 ring atoms of which one or two is the nitrogen atom or atoms and 0 or 1 is an additional hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms;

groups of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16}NHZ$
in which n, Y, R^{16} and R^{19} are as defined above and Z represents a group of formula $-COOR^{17}$, in which R^{17} is as defined above,
a group of formula $-COR^{16}$, in which R^{16} is as defined above, or a group of formula $-SO_2R^{16}$, in which R^{16} is as defined above;

groups of formula $-(CH_2)_nNR^{19}C(=NR^{20})NHR^{20}$
in which n and R^{19} are as defined above and the two symbols R^{20} are independently selected from R^{16}, cyano groups, nitro groups, groups of formula $-COOR^{17}$, in which R^{17} is as defined above, and groups of formula $-COR^{16}$, in which R^{16} is as defined above;

groups of formula $-(CH_2)_nNR^{19}C(=NR^{20})R^{16}$
in which n, R^{16}, R^{19} and R^{20} are as defined above;

groups of formula $-(CH_2)_nNR^{19}SO_mR^{16}$
in which n, R^{16} and R^{19} are as defined above and m is 1 or 2;

groups of formula $-CONHR^{16}$
in which R^{16} is as defined above; and

groups of formula $-COOR^{17}$
in which R^{17} is as defined above;

substituents (a) :
halogen atoms, C_1 - C_4 alkoxy groups, C_1 - C_4 alkylthio groups and C_1 - C_5 alkanoyloxy groups;

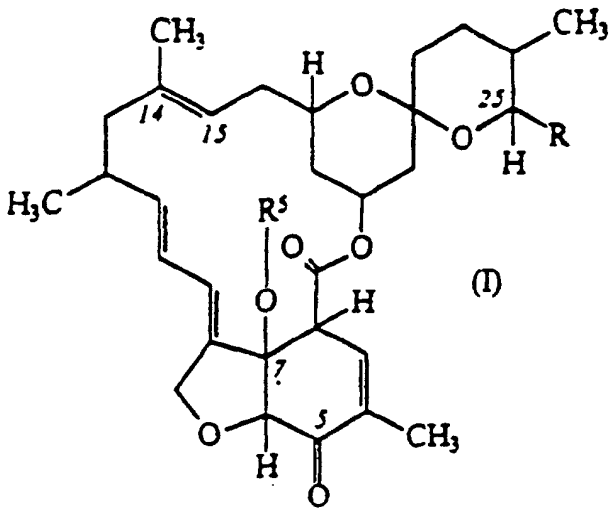
substituents (b) :
C_3 - C_8 cycloalkyl groups; C_1 - C_4 alkoxy groups; C_1 - C_4 alkylthio groups; C_2 - C_5 cyanoalkylthio groups; C_2 - C_5 alkoxycarbonyl groups; halogen atoms; cyano groups; nitro groups; amino groups; carbocyclic aryl groups having from 6 to 10 carbon atoms and being unsubstituted or having at least one substituent selected from substituents (c), defined below; aromatic heterocyclic groups
having from 5 to 8 ring atoms of which from 1 to 4 are hetero-atoms selected from nitrogen, oxygen and sulphur hetero-atoms, the heterocyclic group being monocyclic or fused either to a benzene ring or to a heterocyclic

group which has 5 or 6 ring atoms of which from 1 to 3 are nitrogen hetero-atoms and being unsubstituted or having at least one substituent selected from substituents (c), defined below; and aryloxy and arylthio groups in which the aryl part has from 6 to 10 carbon atoms and is unsubstituted or has at least one substituent selected from substituents (c), defined below;

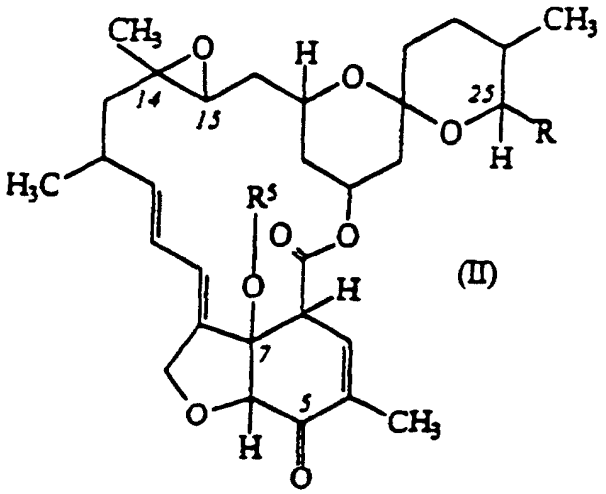
substituents (c) :
C_1 - C_4 alkyl groups, C_1 - C_4 alkoxy groups, C_1 - C_4 alkylthio groups, C_1 - C_5 alkanoyloxy groups, C_2 - C_5 alkoxycarbonyl groups, halogen atoms, cyano groups, nitro groups, amino groups, mono- and di-alkylamino groups in which the or each alkyl part is C_1 - C_4, carbamoyl groups, mono and dialkylcarbamoyl groups in which the or each alkyl part is C_1 - C_4, and C_1 - C_5 alkanoylamino groups;

which process comprises the steps:

A. epoxidising a compound of formula (I) using a reagent system comprising effective amounts of potassium peroxymonosulphate and one or more ketones:

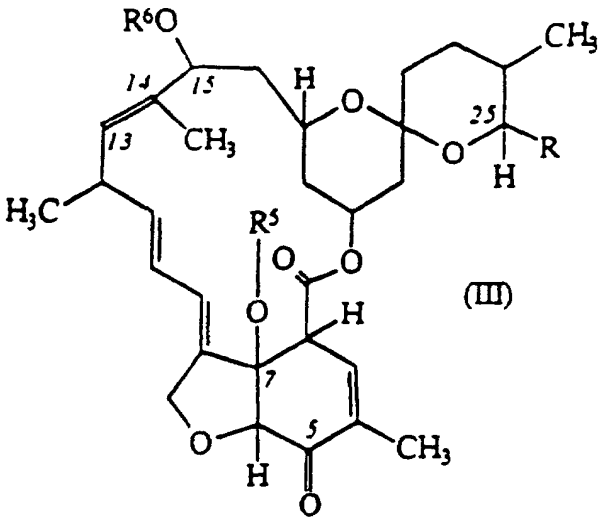


wherein R is as defined above and R^5 represents a hydrogen atom or a group of formula $-SiR^2R^3R^4$, in which R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 6 carbon atoms;
to give a compound of formula (II) :



wherein R and R^5 are as defined above;

B. subjecting the resulting compound of formula (II) to a ring-opening etherification reaction to give a compound of formula (III) :



(III)

wherein R and R^5 are as defined above and R^6 represents a group of formula $-SiR^7R^8R^9$, wherein R^7, R^8 and R^9 are each independently selected from alkyl groups having from 1 to 6 carbon atoms, phenyl groups and benzyl groups;

and

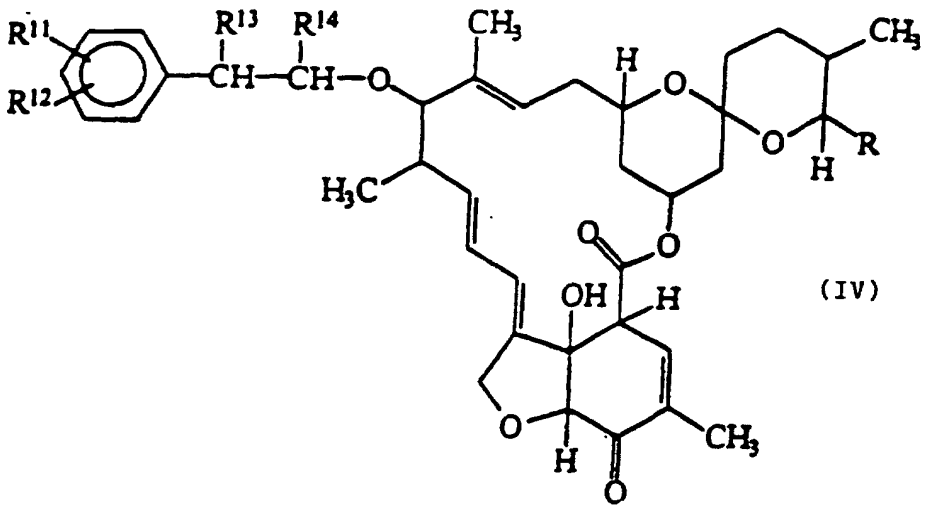
C. reacting the resulting compound of formula (III) with a compound of formula $R^{10}OH$ to give said compound of formula (VIIa).

2. A process according to Claim 1, wherein R^5 represents a trimethylsilyl group.

3. A process according to Claim 1, wherein R^5 represents a hydrogen atom.

4. A process according to any preceding claim, wherein R^{10} represents a 4-(N-methanesulphonyl-N-methylamino) phenylethyl group.

5. A process according to Claim 1, wherein the compound of formula (VIIa) is a compound of formula (IV) :



(IV)

in wich:

R is as defined in Claim 1,
R^{11} and R^{12} are independently selected from: hydrogen atoms; halogen atoms; cyano groups; nitro groups; C_1 - C_4 alkyl groups; substituted C_1 - C_4 alkyl groups having at least one substituent selected from substituents (a), defined below; C_1 - C_4 alkoxy groups; C_2 - C_6 alkoxyalkoxy groups; groups of formula $-(CH_2)_nNHR^{19}$,
in which: n represents 0 or the integer 1 or 2, and R^{19} represents a hydrogen atom or a C_1 - C_4 alkyl group;
groups of formula $-(CH_2)_nNR^{19}C(=O)R^{16}$,
in which:

n and R^{19} are as defined above, and

R^{16} represents: a hydrogen atom; a C_1 - C_4 alkyl group; a substituted C_1 - C_4 alkyl group having at least one substituent selected from substituents (b), defined below; a C_2 - C_8 aliphatic hydrocarbon group having one or two ethylenically unsaturated carbon-carbon double bonds, the group being unsubstituted or having at least one substituent selected from substituents (b), defined below; a C_2 - C_8 alkynyl group; a substituted C_2 - C_8 alkynyl group having at least one substituent selected from substituents (b), defined below; a C_3 - C_8 cycloalkyl group; a substituted C_3 - C_8 cycloalkyl group having at least one substituent selected from substituents (c), defined below; a carbocyclic aryl group having from 6 to 14 ring carbon atoms and being unsubstituted or having at least one substituent selected from substituents (c), defined below; or a heterocyclic group having from 3 to 6 ring atoms of which at least one is a hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms, the heterocyclic group being monocyclic or fused to one or two benzene rings and being unsubstituted or having at least one substituent selected from substituents (c), defined below;

groups of formula $-(CH_2)_nNR^{19}COCOR^{16}$
in which n, R^{16} and R^{19} are as defined above;
groups of formula $-(CH_2)_nR^{19}COCOOR^{17}$
in which n and R^{19} are as defined above and R^{17} represents a C_1 - C_4 alkyl group, a C_3 - C_8 cycloalkyl group or an aralkyl group as defined below;
groups of formula $-(CH_2)_nNR^{19}CHR^{16}NHCOR^{16}$
in which n, R^{16} and R^{19} are as defined above;
groups of formula $-(CH_2)_nNR^{19}CHR^{16}NHCONHR^{16}$
in which n, R^{16} and R^{19} are as defined above;
groups of formula $-(CH_2)_nNR^{19}CHR^{16}NHCOOR^{17}$
in which n, R^{16}, R^{17} and R^{19} are as defined above;
groups of formula $-(CH_2)_nNR^{19}C(=Y)YR^{16}$
in which n, R^{16} and R^{19} are as defined above and the two symbols Y are independently selected from

oxygen and sulphur atoms;
groups of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16'}R^{16'}$
in which n, Y and R^{19} are as defined above, and the two symbols $R^{16'}$ are independently selected from R^{16}, or the two, together with the nitrogen atom to which they are attached, form a heterocyclic group having from 3 to 7 ring atoms of which one is the nitrogen atom and 0 or 1 is an additional hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms;
groups of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16''}NR^{16''}R^{16''}$
in which n, Y and R^{19} are as defined above, and each of the symbols $R^{16''}$ is independently selected from R^{16}, or any two of the symbols $R^{16''}$, together with the nitrogen atom to which each is attached, forms a heterocyclic group having from 3 to 7 ring atoms of which one or two is the nitrogen atom or atoms and 0 or 1 is an additional hetero-atom selected from nitrogen, oxygen and sulphur hetero-atoms;
groups of formula $-(CH_2)_nNR^{19}C(=Y)NR^{16}NHZ$
in which n, Y, R^{16} and R^{19} are as defined above and Z represents

a group of formula $-COOR^{17}$, in which R^{17} is as defined above,

a group of formula $-COR^{16}$, in which R^{16} is as defined above, or

a group of formula $-SO_2R^{16}$, in which R^{16} is as defined above;

groups of formula $-(CH_2)_nNR^{19}C(=NR^{20})NHR^{20}$
in which n and R^{19} are as defined above and the two symbols R^{20} are independently selected from R^{16}, cyano groups, nitro groups, groups of formula $-COOR^{17}$, in which R^{17} is as defined above, and groups of formula $-COR^{16}$, in which R^{16} is as defined above;
groups of formula $-(CH_2)_nNR^{19}C(=NR^{20})R^{16}$
in which n, R^{16}, R^{19} and R^{20} are as defined above;
groups of formula $-(CH_2)_nNR^{19}SO_mR^{16}$
in which n, R^{16} and R^{19} are as defined above and m is 1 or 2;
groups of formula $-CONHR^{16}$
in which R^{16} is as defined above; and
groups of formula $-COOR^{17}$
in which R^{17} is as defined above; and
R^{13} and R^{14} are independently selected from hydrogen atoms, C_1 - C_4 alkyl groups and C_1 - C_4 alkoxy groups;
the aralkyl groups have from 1 to 4 carbon atoms in the alkyl part and from 6 to 10 ring atoms in the aryl part, which is a carbocyclic aryl group which is unsubstituted or has at least one substituent selected from substituents (c), defined below;

substituents (a) :
halogen atoms, C_1 - C_4 alkoxy groups, C_1 - C_4 alkylthio groups and C_1 - C_5 alkanoyloxy groups;

substituents (b) :
C_3 - C_8 cycloalkyl groups; C_1 - C_4 alkoxy groups; C_1 - C_4 alkylthio groups; C_2 - C_5 cyanoalkylthio groups; C_2 - C_5 alkoxycarbonyl groups; halogen atoms; cyano groups; nitro groups; amino groups; carbocyclic aryl groups having from 6 to 10 carbon atoms and being unsubstituted or having at least one substituent selected from substituents (c), defined below; aromatic heterocyclic groups having from 5 to 8 ring atoms of which from 1 to 4 are hetero-atoms selected from nitrogen, oxygen and sulphur hetero-atoms, the heterocyclic group being monocyclic or fused either to a benzene ring or to a heterocyclic group which has 5 or 6 ring atoms of which from 1 to 3 are nitrogen hetero-atoms and being unsubstituted or having at least one substituent selected from substituents (c), defined below; and aryloxy and arylthio groups in which the aryl part has from 6 to 10 carbon atoms and is unsubstituted or has at least one substituent selected from substituents (c), defined below;

substituents (c) :
C_1 - C_4 alkyl groups, C_1 - C_4 alkoxy groups, C_1 - C_4 alkylthio groups, C_1 - C_5 alkanoyloxy groups, C_2 - C_5 alkoxycarbonyl groups, halogen atoms, cyano groups, nitro groups, amino groups, mono- and di-alkylamino groups in which the or each alkyl

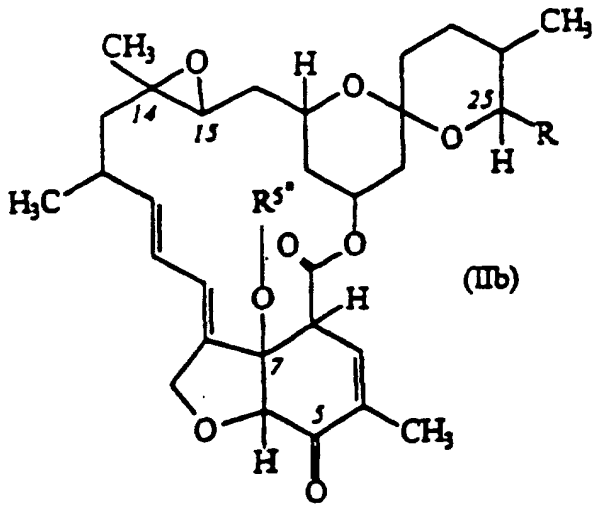
part is C_1 - C_4, carbamoyl groups, mono- and dialkylcarbamoyl groups in which the or each alkyl part is C_1 - C_4, and C_1 - C_5 alkanoylamino groups;

and salts thereof.

6. A process according to any preceding claim, wherein the compound of formula (IV) or (VIIa) is further hydrogenated to give a compound having a hydroxyl group at the 5- position.

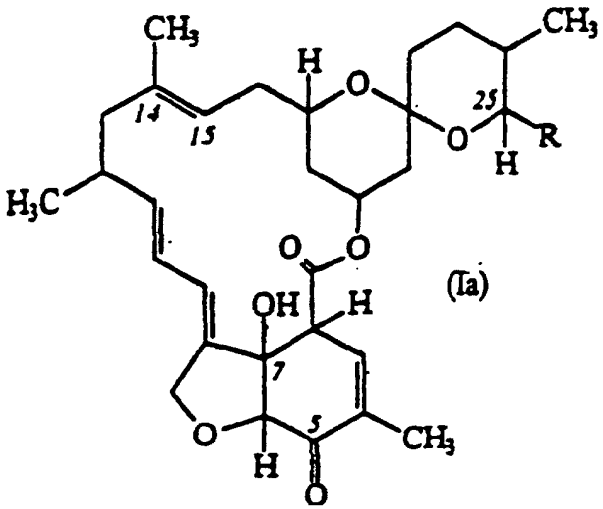
7. A process according to Claim 6, wherein the compound of formula (IV) or (VIIa) is 5-oxo-13-{2-[4-(N-methanesulphonyl-N-methylamino)phenyl]ethoxy}milbemycin A_4 and is further hydrogenated to give 13-{2-[4-(N-methanesulphonyl-N-methylamino)phenyl]ethoxy}milbemycin A_4.

8. A process for the preparation of a compound of formula (IIIb) :



(IIIb)

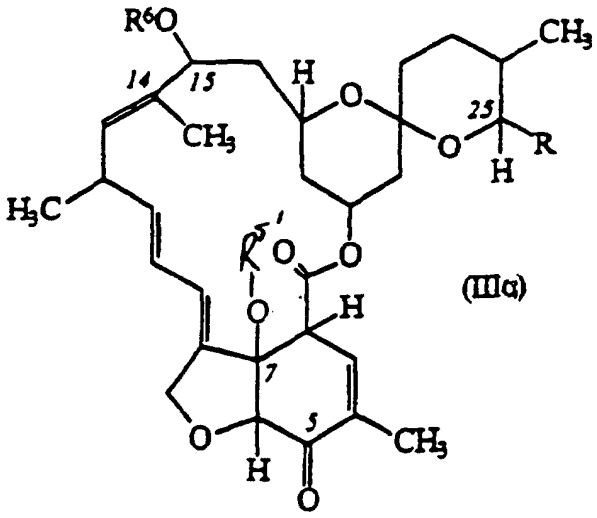
in which R is as defined in Claim 1; and $R^{5''}$ represents a hydrogen atom;
which process comprises epoxidising a compound of formula (Ia) :



(Ia)

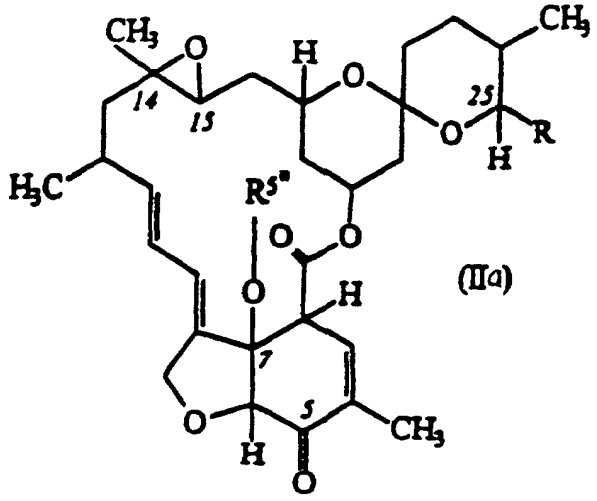
wherein R is as defined above, said epoxidisation being effected by a reagent system comprising effective amounts of potassium peroxymonosulphate and one or more ketones.

9. A process for the preparation of a compound of formula (IIIa) :



(IIIa)

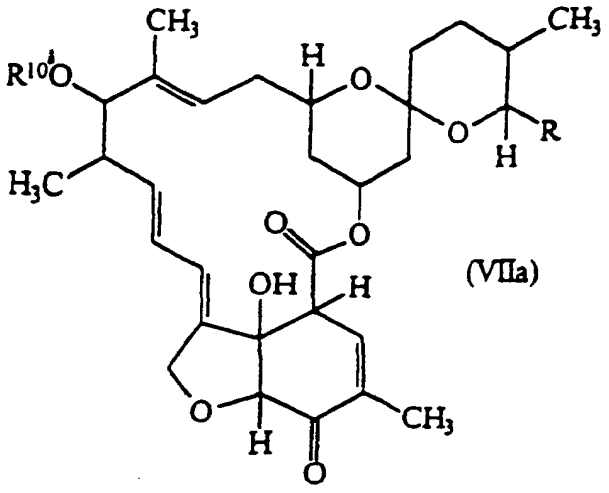
in which R is as defined in Claim 1, $R^{5'}$ represents a group of formula $-SiR^2R^3R^4$, in which R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 4 carbon atoms, and R^6 represents a group of formula $SiR^7R^8R^9$, wherein R^7 is selected from alkyl groups having from 1 to 4 carbon atoms, and R^8 and R^9 are each independently selected from alkyl groups having from 1 to 4 carbon atoms, phenyl groups and benzyl groups; which process comprises subjecting a compound of formula (IIa) :



(IIa)

wherein R and $R^{5'}$ are as defined above;
to a ring-opening etherification reaction.

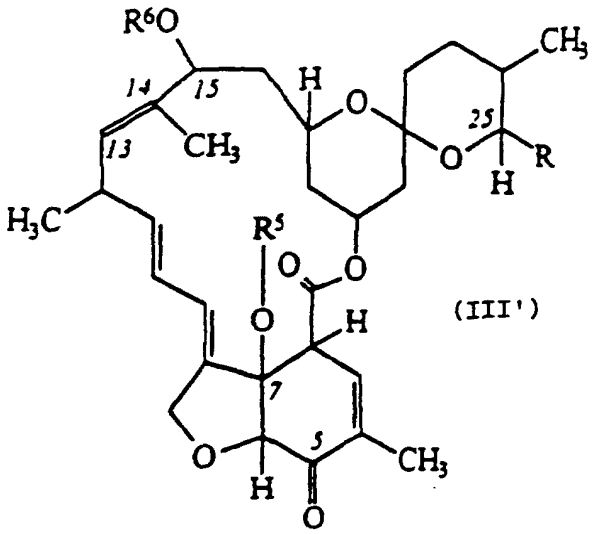
10. A process for preparing a compound of formula (VIIa) :



(VIIa)

wherein R is as defined in Claim 1 and $R^{10'}$ represents a 4-(N-methanesulphonyl-N-methylamino)phenylethyl group,

which process comprises reacting a compound of formula (III') :



(III')

in which R is as defined in Claim 1, R^5 represents a hydrogen atom or a group of formula $-SiR^2R^3R^4$, wherein R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 4 carbon atoms and R^6 represents a hydrogen atom or a group of formula $-SiR^7R^8R^9$, wherein R^7 is selected from alkyl groups having from 1 to 4 carbon atoms, and R^8 and R^9 are each independently selected from alkyl groups having from 1 to 4 carbon atoms, phenyl groups and benzyl groups,

with a compound of formula $R^{10'}OH$ in the presence of an acid.

11. A process according to Claim 10, wherein the compound of formula (VIIa) is further hydrogenated to give a compound having a hydroxyl group at the 5- position.

12. A process according to Claim 10 or Claim 11 wherein R^5 represents a hydrogen atom.

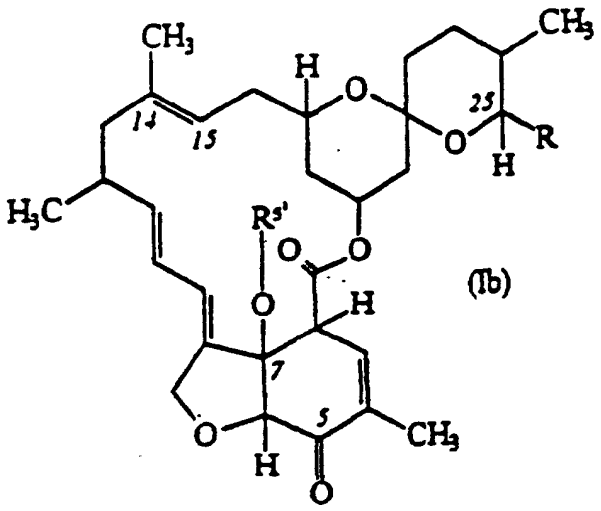
13. A process according to Claim 10 or Claim 11 wherein R^5 represents a trimethylsilyl group.

14. A process according to any preceding claim, wherein R^6 represents a trimethylsilyl group.

15. A process according to any one of Claims 1 to 7 and 9 to 14, wherein R represents a methyl group or an ethyl group.

16. A process according to any one of Claims 1 to 8 and 11 to 15 wherein the compound of formula (VIIa) is 5-oxo-13-{2-[4-(N-methanesulphonyl-N-methylamino)phenyl]ethoxy}milbemycin A_4 and is further hydrogenated to give 13-{2-[4-(N-methanesulphonyl-N-methylamino)phenyl]-ethoxy}milbemycin A_4.

17. A compound of formula (Ib) :

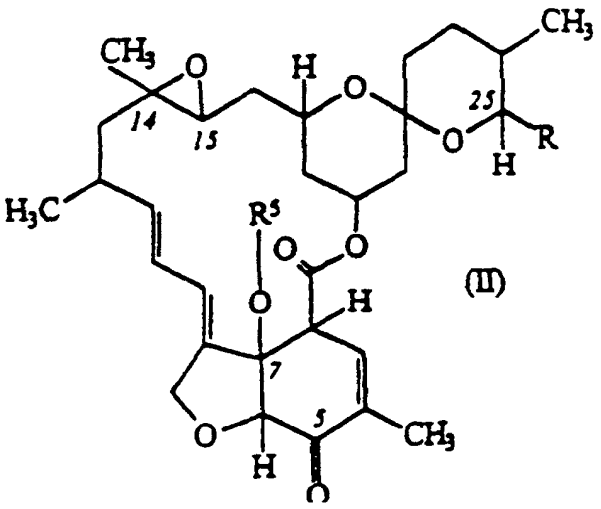


(Ib)

wherein R represents a methyl group, an ethyl group, an isopropyl group or a sec-butyl group, and $R^{5'}$ represents a group of formula $-SiR^2R^3R^4$, wherein R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 4 carbon atoms.

18. A compound according to Claim 17, wherein $R^{5'}$ represents a trimethylsilyl group.

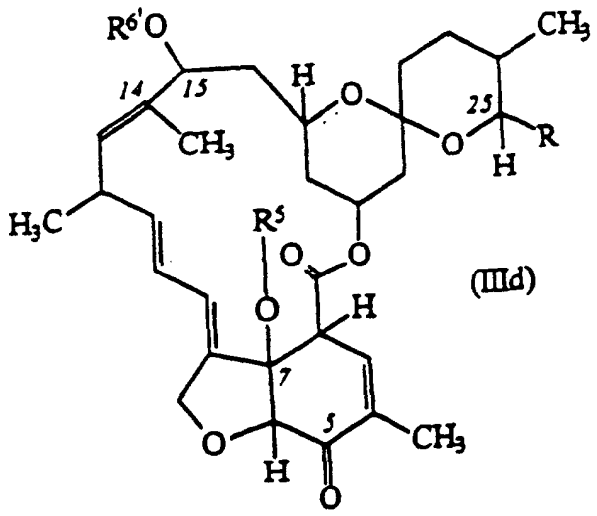
19. A compound of formula (II) :



(II)

wherein R represents a methyl group, an ethyl group, an isopropyl group or a sec-butyl group, and R^5 represents a hydrogen atom or a group of formula $-SiR^2R^3R^4$, wherein R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 4 carbon atoms.

20. A compound of formula (IIId) :



(IIId)

wherein R represents a methyl group, an ethyl group, an isopropyl group or a sec-butyl group, R^5 represents a hydrogen atom or a group of formula $-SiR^2R^3R^4$, wherein R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 4 carbon atoms and $R^{6'}$ represents a hydrogen atom or a group of formula $-SiR^7R^8R^9$, wherein R^7 is selected from alkyl groups having from 1 to 4 carbon atoms, and R^8 and and R^9 are each independently selected from alkyl groups having from 1 to 4 carbon atoms, phenyl groups and benzyl groups.

21. A compound according to Claim 19 or 20, wherein R^5 represents a group of formula $-SiR^2R^3R^4$, wherein R^2, R^3 and R^4 each independently represents an alkyl group having from 1 to 4 carbon atoms.

22. A compound according to Claim 21, wherein R^5 represents a trimethylsilyl group.

23. A compound according to Claim 19 or 20, wherein R^5 represents a hydrogen atom.

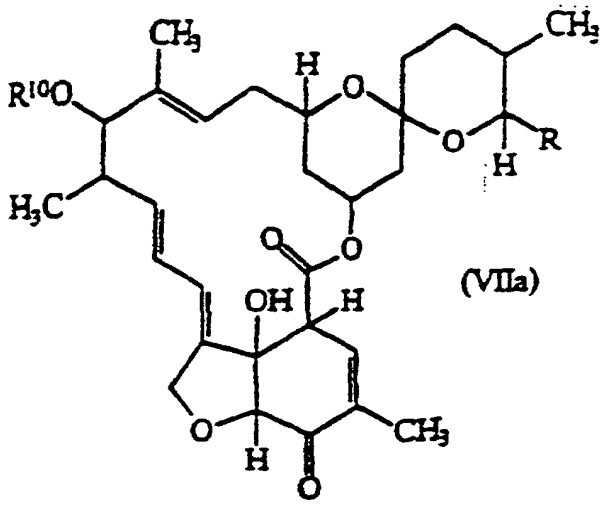
24. A compound according to any of Claims 20 to 23, wherein $R^{6'}$ represents a group of formula $-SiR^7R^8R^9$, wherein R^7 is selected from alkyl groups having from 1 to 4 carbon atoms, and R^8 and R^9 are each independently selected from alkyl groups having from 1 to 4 carbon atoms, phenyl groups and benzyl groups.

25. A compound according to Claim 24, wherein $R^{6'}$ represents a trimethylsilyl group.

26. A compound according to any of Claims 17 to 25, wherein R represents a methyl group or an ethyl group.

Patentansprüche

1. Verfahren zur Herstellung einer Verbindung der Formel (VIIa):



(VIIa)

worin R eine Methylgruppe, eine Ethylgruppe, eine Isopropylgruppe oder eine sec-Butylgruppe darstellt, und R^{10} eine Alkylgruppe mit 1 bis 20 Kohlenstoffatomen, eine Alkenylgruppe mit 2 bis 6 Kohlenstoffatomen, eine Alkinylgruppe mit 2 bis 6 Kohlenstoffatomen oder eine Aralkylgruppe darstellt, worin der Alkylteil 1 bis 10 Kohlenstoffatome hat und unsubstituiert oder mit 1 oder 2 Alkoxygruppen mit je 1 bis 4 Kohlenstoffatomen substituiert ist und der Arylteil 6 bis 10 Ringkohlenstoffatome hat und unsubstituiert oder mit mindestens einem Substituenten substituiert ist, der unter den folgenden Substituenten ausgewählt ist:

Halogenatome, Cyangruppen, Nitrogruppen, C_1-C_4-Alkylgruppen, substituierte C_1-C_4-Alkylgruppen mit mindestens einem Substituenten, der unter den nachstehend definierten Substituenten (a) ausgewählt ist, C_1-C_4-Alkoxygruppen, C_2-C_6-Alkoxyalkoxygruppen, Gruppen der Formel $-(CH_2)_nNHR^{19}$, worin n 0 oder die ganze Zahl 1 oder 2 darstellt und R^{19} ein Wasserstoffatom oder eine C_1-C_4-Alkylgruppe darstellt,

Gruppen der Formel $-(CH_2)_nNR^{19}C(=O)R^{16}$
worin:

n und R^{19} wie vorstehend definiert sind und

R^{16} darstellt: ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe mit mindestens einem Substituenten, der unter den nachstehend definierten Substituenten (b) ausgewählt ist, eine C_2-C_8 aliphatische Kohlenwasserstoffgruppe mit einer oder zwei ethylenisch ungesättigten Kohlenstoff-Kohlenstoff-Doppelbindungen,

wobei die Gruppe unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (b) ausgewählt ist, eine C_2-C_8-Alkinylgruppe, eine substituierte C_2-C_8-Alkinylgruppe mit mindestens einem Substituenten, der unter den nachstehend definierten Substituenten (c) ausgewählt ist, eine C_3-C_8-Cycloalkylgruppe, eine substituierte C_3-C_8-Cycloalkylgruppe mit mindestens einem Substituenten, der unter den nachstehend definierten (c) ausgewählt ist, eine carbocyclische Arylgruppe mit 6 bis 14 Ringkohlenstoffatomen, die unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist, oder eine heterocyclische Gruppe mit 3 bis 6 Ringatomen, unter denen mindestens eines ein Heteroatom ist, das unter Stickstoff-, Sauerstoff- und Schwefelheteroatomen ausgewählt ist, wobei die heterocyclische Gruppe monocyclisch ist oder an einen oder zwei Benzolringen kondensiert ist und unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist,
Gruppen der Formel $-(CH_2)_nNR^{19}COCOR^{16}$
worin n, R^{16} und R^{19} wie vorstehend definiert sind,
Gruppen der Formel $-(CH_2)_nR^{19}COCOOR^{17}$
worin n und R^{19} wie vorstehend definiert sind und R^{17} eine C_1-C_4-Alkylgruppe, eine C_3-C_8-Cycloalkylgruppe oder eine Aralkylgruppe mit 1 bis 4 Kohlenstoffatomen im Alkylteil und 6 bis 10 Ringatomen im Arylteil darstellt, welcher eine carbocyclische Arylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist,

Gruppen der Formel $-(CH_2)_nNR^{19}CHR^{16}NHCOR^{16}$
worin n, R^{16} und R^{19} wie vorstehend definiert sind,
Gruppen der Formel $-(CH_2)_nNR^{19}CHR^{16}NHCONHR^{16}$
worin n, R^{16} und R^{19} wie vorstehend definiert sind,
Gruppen der Formel $-(CH_2)_nNR^{19}$ $CHR^{16}NHCOOR^{17}$
worin n, R^{16}, R^{17} und R^{19} wie vorstehend definiert sind,
Gruppen der Formel $-(CH_2)_nNR^{19}C(=Y)YR^{16}$
worin n, R^{16} und R^{19} wie vorstehend definiert sind und die zwei Symbole Y unabhängig voneinander unter Sauerstoffund Schwefelatomen ausgewählt sind,
Gruppen der Formel - $(CH_2)_nNR^{19}C(=Y)NR^{16'}R^{16'}$
worin n, Y und R^{19} wie vorstehend definiert sind und die zwei Gruppen $R^{16'}$ unabhängig voneinander unter R^{16} ausgewählt sind oder die zwei Gruppen $R^{16'}$ zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine heterocyclische Gruppe mit 3 bis 7 Ringatomen darstellen, von denen eines das Stickstoffatom ist und keines oder eines ein zusätzliches Heteroatom ist, das unter Stickstoff-, Sauerstoff- und Schwefelheteroatomen ausgewählt ist,
Gruppen der Formel $-(CH_2)_nNR^{19}C(=Y)NR^{16''}NR^{16''}R^{16''}$
worin n, Y und R^{19} wie vorstehend definiert sind und jede der Gruppen $R^{16''}$ unabhängig voneinander unter R^{16} ausgewählt ist oder beliebige zwei der Gruppen $R^{16''}$ zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine heterocyclische Gruppe mit 3 bis 7 Ringatomen bilden, von denen eines oder zwei das Stickstoffatom ist oder die Stickstoffatome sind und keines oder eines ein zusätzliches Heteroatom ist, das unter Stickstoff-, Sauerstoff- und Schwefelheteroatomen ausgewählt ist,
Gruppen der Formel $-(CH_2)_nNR^{19}C(=Y)NR^{16}NHZ$
worin n, Y, R^{16} und R^{19} wie vorstehend definiert sind und Z eine Gruppe der Formel $-COOR^{17}$, worin R^{17} wie vorstehend definiert ist, eine Gruppe der Formel $-COR^{16}$, worin R^{16} wie vorstehend definiert ist oder eine Gruppe der Formel $-SO_2R^{16}$ darstellt, worin R^{16} wie vorstehend definiert ist,
Gruppen der Formel $-(CH_2)_nNR^{19}C(=NR^{20})NHR^{20}$
worin n und R^{19} wie vorstehend definiert sind und die zwei Gruppen R^{20} unabhängig voneinander unter R^{16}, Cyangruppen, Nitrogruppen, Gruppen der Formel $-COOR^{17}$, worin R^{17} wie vorstehend definiert ist, und Gruppen der Formel COR^{16} ausgewählt sind, worin R^{16} wir vorstehend definiert ist,
Gruppen der Formel $-(CH_2)_nNR^{19}C(=NR^{20})R^{16}$
worin n, R^{16}, R^{19} und R^{20} wie vorstehend definiert sind,
Gruppen der Formel $-(CH_2)_nNR^{19}SO_mR^{16}$
worin n, R^{16} und R^{19} wie vorstehend definiert sind und m 1 oder ist,
Gruppen der Formel $-CONHR^{16}$
worin R^{16} wie vorstehend definiert ist und
Gruppen der Formel $-COOR^{17}$
worin R^{17} wie vorstehend definiert ist,

Substituenten (a):

Halogenatome, C_1-C_4-Alkoxygruppen, C_1-C_4-Alkylthiogruppen und C_1-C_5-Alkanoyloxygruppen;

Substituenten (b):

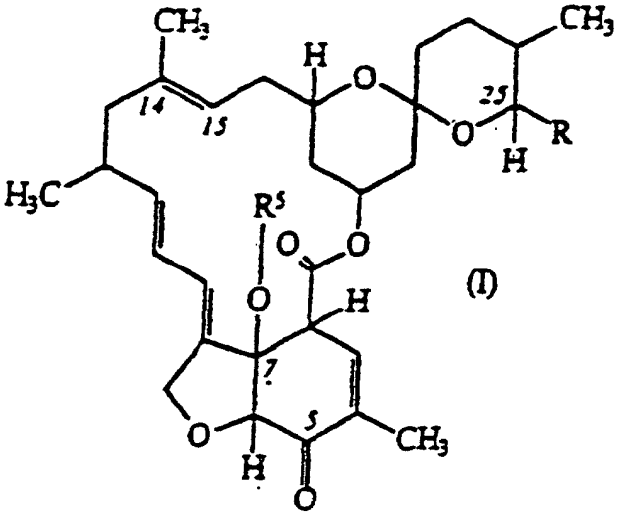
C_3-C_8-Cycloalkylgruppen, C_1-C_4-Alkoxygruppen, C_1-C_4-Alkylthiogruppen, C_2-C_5-Cyanalkylthiogruppen, C_2-C_5-Alkoxycarbonylgruppen, Halogenatome, Cyangruppen, Nitrogruppen, Aminogruppen, carbocyclische Arylgruppen mit 6 bis 10 Kohlenstoffatomen, die unsubstituiert sind oder mindestens einen Substituenten haben, der unter den nachstehend definierten Substituenten (c) ausgewählt ist, aromatische heterocyclische Gruppen mit 5 bis 8 Ringatomen, von denen 1 bis 4 Heteroatome sind, die unter Stickstoff-, Sauerstoff- und Schwefelheteroatomen ausgewählt sind, wobei die heterocyclische Gruppe monocyclisch ist oder entweder an einen Benzolring oder an eine heterocyclische Gruppe kondensiert ist, die 5 oder 6 Ringatome hat, von denen 1 bis 3 Stickstoffheteroatome sind, und die unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist, und Aryloxyund Arylthiogruppen, worin der Arylteil 6 bis 10 Kohlenstoffatome hat und unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist;

Substituenten (c):

C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen, C_1-C_4-Alkylthiogruppen, C_1-C_5-Alkanoyloxygruppen, C_2-C_5-Alkoxycarbonylgruppen, Halogenatome, Cyangruppen, Nitrogruppen, Aminogruppen, Mono- und Dialkylaminogruppen, worin der oder jeder Alkylteil C_1-C_4 ist, Carbamoylgruppen, Mono- und Dialkylcarbamoylgruppen, worin der oder jeder Alkylteil C_1-C_4 ist, und C_1-C_5-Alkanoylaminogruppen;

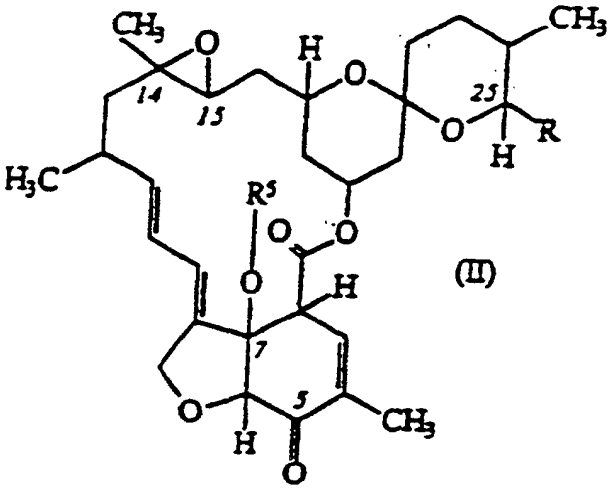
wobei das Verfahren die folgenden Stufen umfaßt:

A. Epoxidieren einer Verbindung der Formel (I) unter Einsatz eines Reagenssystems, das wirksame Mengen Kaliumperoxymonosulfat und eines oder mehrere Ketone enthält:



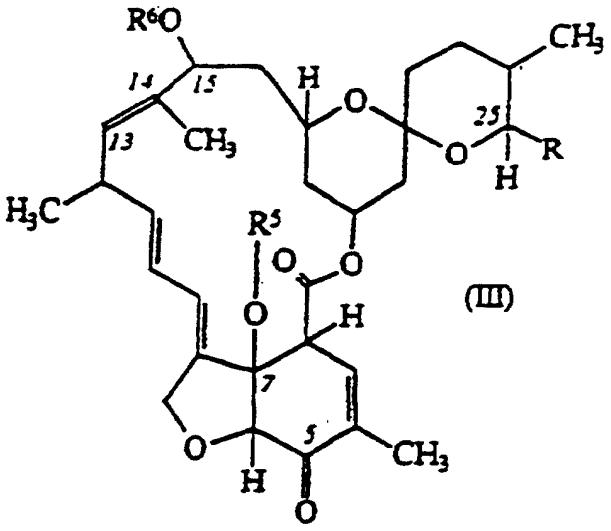
(I)

worin R wie vorstehend definiert ist und R^5 ein Wasserstoffatom oder eine Gruppe der Formel $-SiR^2R^3R^4$ ist, worin R^2, R^3 und R^4 jeweils unabhängig voneinander eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen darstellt; wobei eine Verbindung der Formel (II) erhalten wird:



(II)

worin R und R^5 wie vorstehend definiert sind;
B. unterwerfen der erhaltenen Verbindung der Formel (II) einer Ringöffnungsveretherungsreaktion unter Bildung einer Verbindung der Formel (III):



(III)

worin R und R^5 wie vorstehend definiert sind und R^6 eine Gruppe der Formel $-SiR^7R^8R^9$ darstellt, worin R^7, R^8 und R^9 jeweils unabhängig voneinander unter Alkylgruppen mit 1 bis 6 Kohlenstoffatomen, Phenylgruppen und Benzylgruppen ausgewählt sind;

und

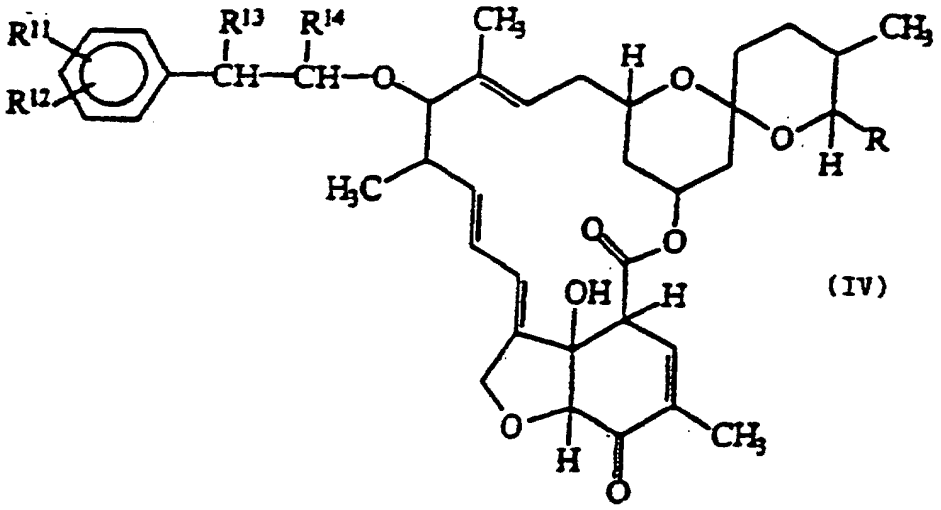
C. Umsetzen der erhaltenen Verbindung der Formel (III) mit einer Verbindung der Formel $R^{10}OH$ unter Bildung der Verbindung der Formel (VIIa).

2. Verfahren nach Anspruch 1, wobei R^5 eine Trimethylsilylgruppe darstellt.

3. Verfahren nach Anspruch 1, wobei R^5 ein Wasserstoffatom darstellt.

4. Verfahren nach einem der vorstehenden Ansprüche, wobei R^{10} eine 4-(N-Methansulfonyl-N-methylamino)phenylethylgruppe darstellt.

5. Verfahren nach Anspruch 1, wobei die Verbindung der Formel (VIIa) eine Verbindung der Formel (IV) ist:



(IV)

worin:

R wie in Anspruch 1 definiert ist,

R^{11} und R^{12} unabhängig voneinander ausgewählt sind unter: Wasserstoffatomen, Halogenatomen, Cyangruppen, Nitrogruppen, C_1-C_4-Alkylgruppen, substituierten C_1-C_4-Alkylgruppen mit mindestens einem Substituenten, der unter den nachstehend definierten Substituenten (a) ausgewählt ist, C_1-C_4-Alkoxygruppen, C_2-C_6-Alkoxyalkoxygruppen, Gruppen der Formel - $(CH_2)_nNHR^{19}$,

worin: n 0 oder die ganze Zahl 1' oder 2 darstellt und R^{19} ein Wasserstoffatom oder eine C_1-C_4-Alkylgruppe darstellt,

Gruppen der Formel -$(CH_2)_nNR^{19}C(=O)R^{16}$,

worin:

n und R^{19} wie vorstehend definiert sind, und

R^{16} darstellt: ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe, eine substituierte C_1-C_4-Alkylgruppe mit mindestens einem Substituenten, der unter den nachstehend definierten Substituenten (b) ausgewählt ist, eine C_2-C_8 aliphatische Kohlenwasserstoffgruppe mit einer oder zwei ethylenisch ungesättigten Kohlenstoff-Kohlenstoff-Doppelbindungen, wobei die Gruppe unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (b) ausgewählt ist, eine C_2-C_8-Alkenylgruppe, eine substituierte C_2-C_8-Alkynylgruppen mit mindestens einem Substituenten, der unter den nachstehend definierten Substituenten (b) ausgewählt ist, eine C_3-C_8-Cycloalkylgruppe, eine substituierte C_3-C_8-Cycloalkylgruppe mit mindestens einem Substituenten, der unter den nachstehend definierten Substituenten (c) ausgewählt ist, eine carbocyclische Arylgruppe mit 6 bis 14 Ringkohlenstoffatomen, die unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist, oder eine heterocyclische Gruppe mit 3 bis 6 Ringatomen, von denen mindestens eines ein Heteroatom ist, das unter Stickstoff-, Sauerstoff- und Schwefelheteroatomen ausgewählt ist, wobei die heterocyclische Gruppe monocyclisch ist oder an einen oder zwei Benzolringe kondensiert ist und unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist,

Gruppen der Formel -$(CH_2)_nNR^{19}COCOR^{16}$

worin n, R^{16} und R^{19} wie vorstehend definiert sind,

Gruppen der Formel -$(CH_2)_nR^{19}COCOOR^{17}$

worin n und R^{19} wie vorstehend definiert sind und R^{17} eine C_1-C_4-Alkylgruppe, eine C_3-C_8-Cycloalkylgruppe oder eine wie nachstehend definierte Aralkylgruppe darstellt,

Gruppen der Formel -$(CH_2)_nNR^{19}CHR^{16}NHCOR^{16}$

worin n, R^{16} und R^{19} wie vorstehend definiert sind,

Gruppen der Formel -$(CH_2)_nNR^{19}CHR^{16}NHCONHR^{16}$

worin n, R^{16} und R^{19} wie vorstehend definiert sind,

Gruppen der Formel -$(CH_2)_nNR^{19}CHR^{16}NHCOOR^{17}$

worin n, R^{16} und R^{19} wie vorstehend definiert sind,

Gruppen der Formel -$(CH_2)_nNR^{19}C(=Y)YR^{16}$

worin n, R^{16} und R^{19} wie vorstehend definiert sind und die zwei Symbole Y unabhängig voneinander unter Sauerstoffund Schwefelatomen ausgewählt sind,

Gruppen der Formel -$(CH_2)_nNR^{19}C(=Y)NR^{16'}R^{16'}$

worin n, Y und R^{19} wie vorstehend definiert sind und die zwei Gruppen $R^{16'}$ unabhängig voneinander unter R^{16} ausgewählt sind oder die zwei Gruppen $R^{16'}$ zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine heterocyclische Gruppe mit 3 bis 7 Ringatomen darstellen, von denen eines das Stickstoffatom ist und keines oder eines ein zusätzliches Heteroatom ist, das unter Stickstoff-, Sauerstoff- und Schwefelheteroatomen ausgewählt ist,

Gruppen der Formel -$(CH_2)_nNR^{19}C(=Y)NR^{16''}NR^{16''}R^{16''}$

worin n, Y und R^{19} wie vorstehend definiert sind und jedes der Gruppen $R^{16"}$ unabhängig voneinander unter R^{16} ausgewählt ist oder beliebige zwei der Gruppen $R^{16"}$ zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine heterocyclische Gruppe mit 3 bis 7 Ringatomen bilden, von denen eines oder zwei das Stickstoffatom ist oder die Stickstoffatome sind und keines oder eines ein zusätzliches Heteroatom ist, das unter Stickstoff-, Sauerstoff- und Schwefelheteroatomen ausgewählt ist,

Gruppen der Formel $-(CH_2)_nNR^{19}C(=Y)NR^{16}NHZ$
worin n, Y, R^{16} und R^{19} wie vorstehend definiert sind und Z eine Gruppe der Formel $-COOR^{17}$, worin R^{17} wie vorstehend definiert ist,
eine Gruppe der Formel $-COR^{16}$, worin R^{16} wie vorstehend definiert ist oder
eine Gruppe der Formel $-SO_2R^{16}$ darstellt, worin R^{16} wie vorstehend definiert ist,

Gruppen der Formel $-(CH_2)_nNR^{19}C(=NR^{20})NHR^{20}$
worin n und R^{19} wie vorstehend definiert sind und die zwei Symbole R^{20} unabhängig voneinander unter R^{16}, Cyangruppen, Nitrogruppen, Gruppen der Formel $-COOR^{17}$, worin R^{17} wie vorstehend definiert ist, und Gruppen der Formel COR^{16} ausgewählt sind, worin R^{16} wie vorstehend definiert ist,

Gruppen der Formel $-(CH_2)_nNR^{19}C(=NR^{20})R^{16}$
worin n, R^{16}, R^{19} und R^{20} wie vorstehend definiert sind,

Gruppen der Formel $-(CH_2)_nNR^{19}SO_mR^{16}$
worin n, R^{16} und R^{19} wie vorstehend definiert sind und m 1 oder ist,

Gruppen der Formel $-CONHR^{16}$
worin R^{16} wie vorstehend definiert ist und

Gruppen der Formel $-COOR^{17}$
orin R^{17} wie vorstehend definiert ist, und

R^{13} und R^{14} unabhängig voneinander unter Wasserstoffatomen, C_1-C_4-Alkylgruppen und C_1-C_4-Alkoxygruppen ausgewählt sind,

die Aralkylgruppen 1 bis 4 Kohlenstoffatome im Alkylteil und 6 bis 10 Ringatome im Arylteil haben, welcher eine carbocyclische Arylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist,

Substituenten (a):

Halogenatome, C_1-C_4-Alkoxygruppen, C_1-C_4-Alkylthiogruppen und C_1-C_5-Alkanoyloxygruppen;

Substituenten (b):

C_3-C_8-Cycloalkylgruppen, C_1-C_4-Alkoxygruppen, C_1-C_4-Alkylthiogruppen, C_2-C_5-Cyanalkylthiogruppen, C_2-C_5-Alkoxycarbonylgruppen, Halogenatome, Cyangruppen, Nitrogruppen, Aminogruppen, carbocyclische Arylgruppen mit 6 bis 10 Kohlenstoffatomen, die unsubstituiert sind oder mindestens einen Substituenten haben, der unter den nachstehend definierten Substituenten (c) ausgewählt ist, aromatische heterocyclische Gruppen mit 5 bis 8 Ringatomen, von denen 1 bis 4 Heteroatome sind, die unter Stickstoff-, Sauerstoff- und Schwefelheteroatomen ausgewählt sind, wobei die heterocyclische Gruppe monocyclisch ist oder entweder an einen Benzolring oder an eine heterocyclische Gruppe kondensiert ist, die 5 oder 6 Ringatome hat, von denen 1 bis 3 Stickstoffheteroatome sind, und die unsubstituiert ist oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist, und Aryloxyund Arylthiogruppen, worin der Arylteil 6 bis 10 Kohlenstoffatome hat, und unsubstituiert ist, oder mindestens einen Substituenten hat, der unter den nachstehend definierten Substituenten (c) ausgewählt ist;

Substituenten (c):

C_1-C_4-Alkylgruppen, C_1-C_4-Alkoxygruppen, C_1-C_4-Alkylthiogruppen, C_1-C_5-Alkanoyloxygruppen, C_2-C_5-

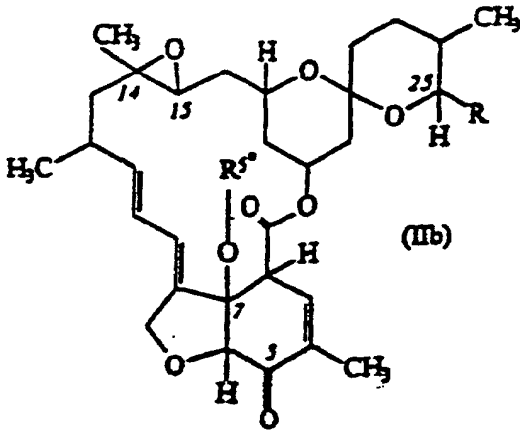
Alkoxycarbonylgruppen, Halogenatome, Cyangruppen, Nitrogruppen, Aminogruppen, Mono- und Dialkylaminogruppen, worin der oder jeder Alkylteil C_1-C_4 ist, Carbamoylgruppen, Mono- und Dialkylcarbamoylgruppen, worin der oder jeder Alkylteil C_1-C_4 ist und C_1-C_5Alkanoylaminogruppen;

und von Salzen davon.

6. Verfahren nach einem der vorstehenden Ansprüche, wobei die Verbindung (IV) oder (VIIa) unter Bildung einer Verbindung mit einer Hydroxygruppe an der 5-Position weiter hydriert wird.

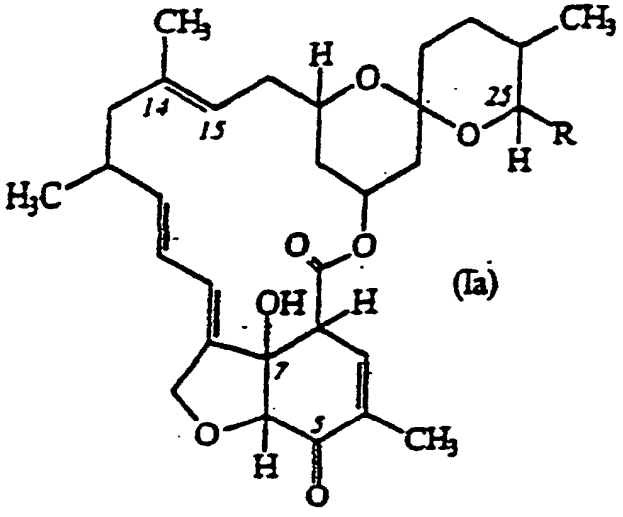
7. Verfahren nach Anspruch 6, wobei die Verbindung der Formel (IV) oder (VIIa) 5-Oxo-13-{2-[4-(N-methansulfonyl-N-methylamino)phenyl]ethoxy}milbemycin A_4 ist und unter Bildung von 13-{2-[4-(N-Methansulfonyl-N-methylamino)phenyl]-ethoxy)milbemycin A_4 weiter hydriert wird.

8. Verfahren zur Herstellung einer Verbindung der Formel (IIb):



(IIb)

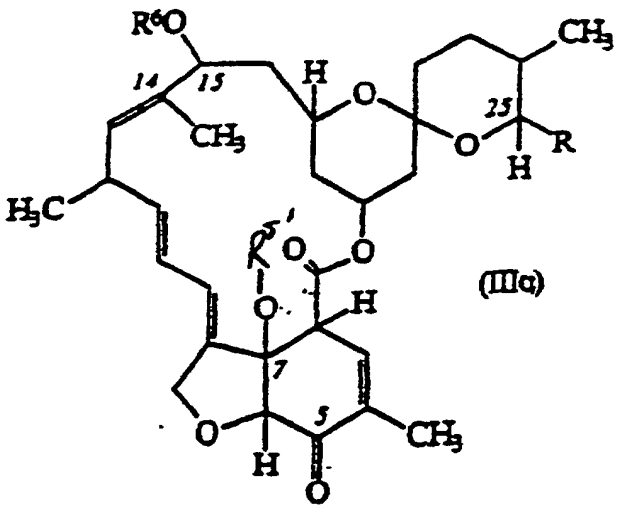
worin R wie in Anspruch 1 definiert ist und $R^{5"}$ ein Wasserstoffatom darstellt;
welches das Epoxidieren einer Verbindung der Formel (Ia) umfaßt:



(Ia)

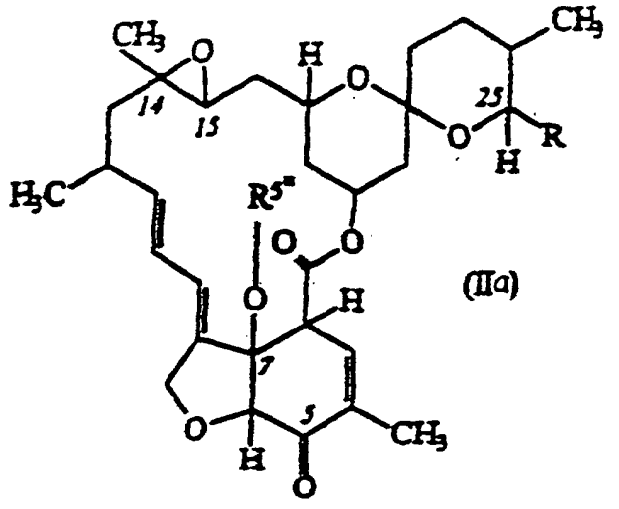
worin R wie vorstehend definiert ist;
wobei die Epoxidierung mit einem Reagenssystem bewirkt wird, das wirksame Mengen Kaliumperoxymonosulfat und ein oder mehrere Ketone enthält.

9. Verfahren zur Herstellung einer Verbindung der Formel (IIIa):



(IIIa)

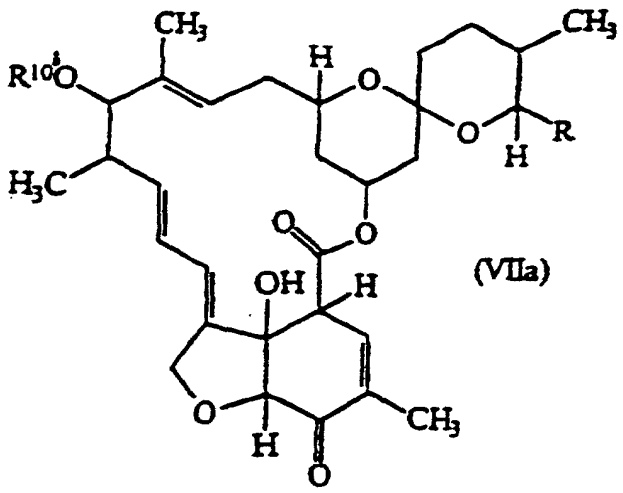
worin R wie in Anspruch 1 definiert ist, $R^{5'}$ eine Gruppe der Formel $-SiR^2R^3R^4$ darstellt, worin R^2, R^3 und R^4 jeweils unabhängig voneinander eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellen, und R^6 eine Gruppe der Formel $SiR^7R^8R^9$ darstellt, worin R^7 unter Alkylgruppen mit 1 bis 4 Kohlenstoffatomen ausgewählt ist, R^8 und R^9 jeweils unabhängig voneinander unter Alkylgruppen mit 1 bis 4 Kohlenstoffatomen, Phenylgruppen und Benzylgruppen ausgewählt sind,
wobei das Verfahren das Unterwerfen einer Verbindung der Formel (IIa):



(IIa)

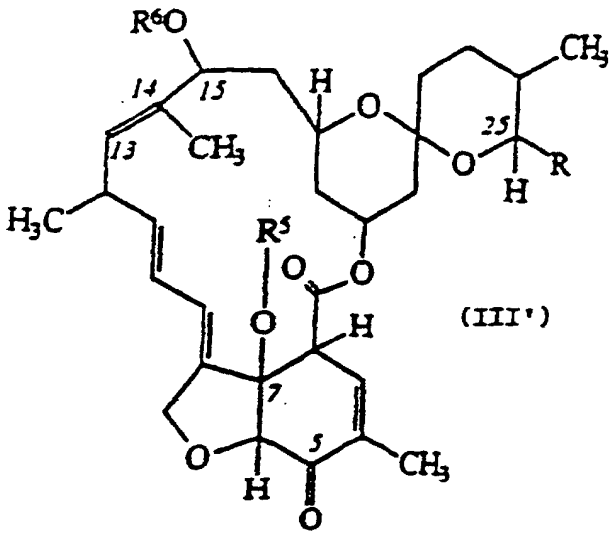
worin R und $R^{5'}$ wie vorstehend definiert sind;
einer Ringöffnungsveretherungsreaktion umfaßt.

10. Verfahren zur Herstellung einer Verbindung der Formel (VIIa):



(VIIa)

worin R wie in Anspruch 1 definiert ist und R^{10} eine 4-(N-Methansulfonyl-N-methylamino)phenylethylgruppe darstellt,
wobei das Verfahren das Umsetzen einer Verbindung der Formel (III'):



(III')

worin R wie in Anspruch 1 definiert ist, R^5 ein Wasserstoffatom oder eine Gruppe der Formel $-SiR^2R^3R^4$ darstellt, worin R^2, R^3 und R^4 jeweils unabhängig voneinander eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellen und R^6 ein Wasserstoffatom oder eine Gruppe der Formel $-SiR^7R^8R^9$ darstellt, worin R^7 unter Alkylgruppen mit 1 bis 4 Kohlenstoffatomen ausgewählt ist und R^8 und R^9 jeweils unabhängig voneinander unter Alkylgruppen mit 1 bis 4 Kohlenstoffatomen, Phenylgruppen und Benzylgruppen ausgewählt sind,
mit einer Verbindung der Formel $R^{10'}OH$ in Anwesenheit einer Säure umfaßt.

11. Verfahren nach Anspruch 10, wobei die Verbindung der Formel (VIIa) unter Bildung einer Verbindung mit einer Hydroxygruppe an der 5-Position weiter hydriert wird.

12. Verfahren nach Anspruch 10 oder 11, wobei R^5 ein Wasserstoffatom darstellt.

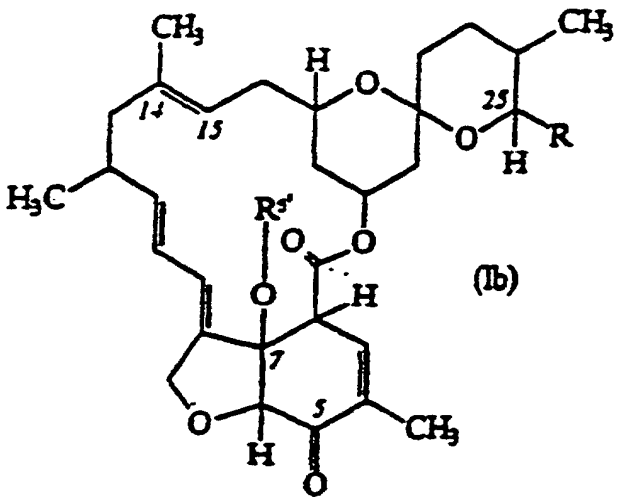
13. Verfahren nach Anspruch 10 oder 11, wobei R^5 eine Trimethylsilylgruppe darstellt.

14. Verfahren nach einem der vorstehenden Ansprüche, wobei R^6 eine Trimethylsilylgruppe darstellt.

15. Verfahren nach einem der Ansprüche 1 bis 7 und 9 bis 14, wobei R eine Methylgruppe oder Ethylgruppe darstellt.

16. Verfahren nach einem der Ansprüche 1 bis 8 und 11 bis 15, wobei die Verbindung der Formel (VIIa) 5-Oxo-13-{2-[4-(N-methansulfonyl-N-methylamino)phenyl]ethoxy}milbemycin A_4 ist und unter Bildung 13-{2-[4-(N-Methansulfonyl-N-methylamino)phenyl]-ethoxy}milbemycin A_4 weiter hydriert wird..

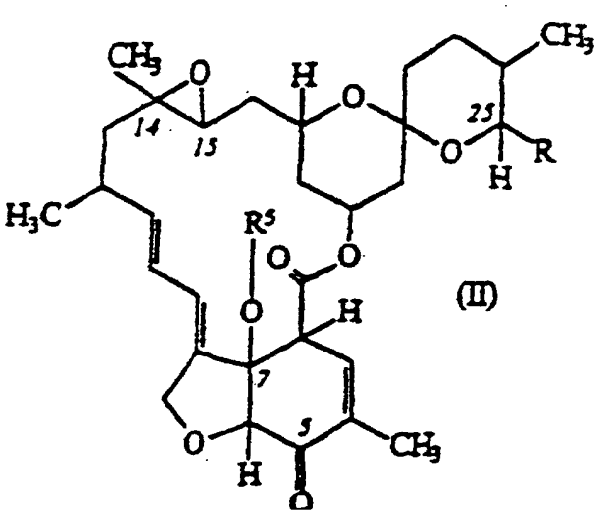
17. Verbindung der Formel (Ib):



worin R eine Methylgruppe, eine Ethylgruppe, eine Isopropylgruppe oder eine sec-Butylgruppe darstellt und $R^{5''}$ eine Gruppe der Formel $-SiR^2R^3R^4$ darstellt, worin R^2, R^3 und R^4 jeweils unabhängig voneinander eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellen.

18. Verbindung nach Anspruch 17, worin $R^{5'}$ eine Trimethylsilylgruppe darstellt.

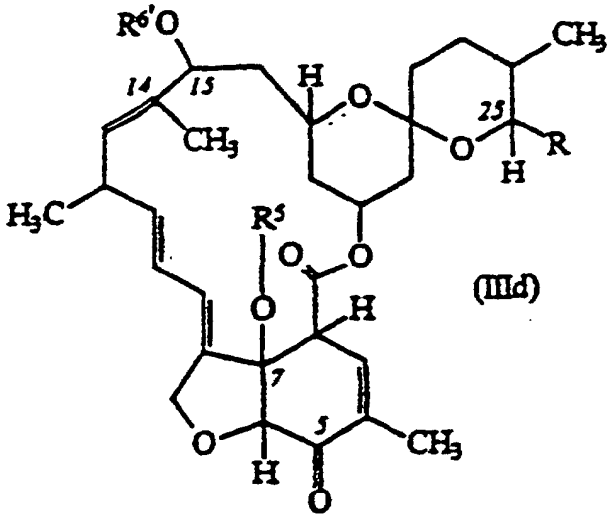
19. Verbindung der Formel (II):



worin R eine Methylgruppe, eine Ethylgruppe, eine Isopropylgruppe oder eine sec-Butylgruppe darstellt und R^5 ein Wasserstoffatom oder eine Gruppe der Formel $-SiR^2R^3R^4$ darstellt, worin R^2, R^3 und R^4 jeweils unabhängig

voneinander eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellen.

20. Verbindung der Formel (IIId):



(IIId)

worin R eine Methylgruppe, eine Ethylgruppe, eine Isopropylgruppe oder eine sec-Butylgruppe darstellt, R^5 ein Wasserstoffatom oder eine Gruppe der Formel $-SiR^2R^3R^4$ darstellt, worin R^2, R^3 und R^4 jeweils unabhängig voneinander eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt und $R^{6'}$ ein Wasserstoffatom oder eine Gruppe der Formel $-SiR^7R^8R^9$ darstellt, worin R^7 unter Alkylgruppen mit 1 bis 4 Kohlenstoffatomen ausgewählt ist und R^8 und R^9 jeweils unabhängig voneinander unter Alkylgruppen mit 1 bis 4 Kohlenstoffatomen, Phenylgruppen und Benzylgruppen ausgewählt sind.

21. Verbindung nach Anspruch 19 oder 20, worin R^5 eine Gruppe der Formel $-SiR^2R^3R^4$ darstellt, worin R^2, R^3 und R^4 jeweils unabhängig voneinander eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen darstellt.

22. Verbindung nach Anspruch 21, worin R^5 eine Trimethylsilylgruppe darstellt.

23. Verbindung nach Anspruch 19 oder 20, worin R^5 ein Wasserstoffatom darstellt.

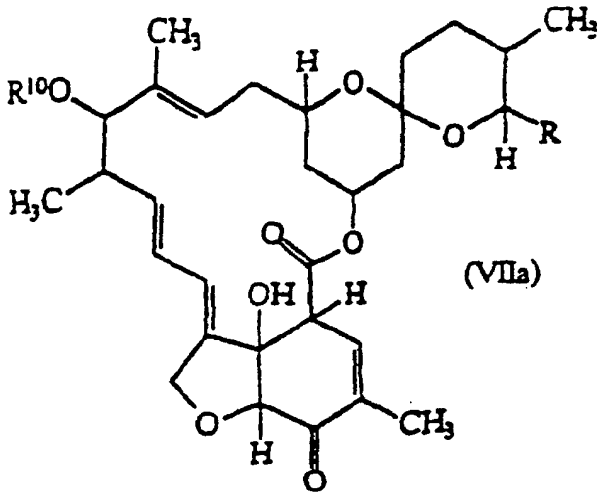
24. Verbindung nach einem der Ansprüche 20 bis 23, worin $R^{6'}$ eine Gruppe der Formel $-SiR^7R^8R^9$ darstellt, worin R^7 Alkylgruppen mit 1 bis 4 Kohlenstoffatomen ausgewählt ist und R^8 und R^9 jeweils unabhängig voneinander unter Alkylgruppen mit 1 bis 4 Kohlenstoffatomen, Phenylgruppen und Benzylgruppen ausgewählt sind.

25. Verbindung nach Anspruch 24, worin $R^{6'}$ eine Trimethylsilylgruppe darstellt.

26. Verbindung nach einem der Ansprüche 17 bis 25, worin R eine Methylgruppe oder eine Ethylgruppe darstellt.

Revendications

1. Procédé pour la préparation d'un composé de formule (VIIa) :



(VIIa)

dans laquelle

R représente un groupe méthyle, un groupe éthyle, un groupe isopropyle ou un groupe sec-butyle, et R^{10} représente un groupe alkyle ayant 1 à 20 atomes de carbone ; un groupe alcényle ayant 2 à 6 atomes de carbone ; un groupe alcynyle ayant 2 à 6 atomes de carbone ; ou un groupe aralkyle dans lequel la portion alkyle compte 1 à 10 atomes de carbone et peut être non substituée ou substituée par 1 ou 2 groupes alcoxy ayant chacun 1 à 4 atomes de carbone, et la portion aryle compte 6 à 10 atomes de carbone cycliques et n'est pas substituée ou est substituée par au moins un substituant choisi parmi :

les atomes d'halogènes ; les groupes cyano ; les groupes nitro ; les groupes alkyle en C_1-C_4 ; les groupes alkyle en C_1-C_4 substitués ayant au moins un substituant choisi parmi les substituants (a), définis ci-dessous ; les groupes alcoxy en C_1-C_4 ; les groupes alcoxyalcoxy en C_2-C_6 ;
les groupes de formule $-(CH_2)_nNHR^{19}$,
dans laquelle :

n représente 0 ou le nombre entier 1 ou 2, et
R^{19} représente un atome d'hydrogène ou un groupe alkyle en C_1-C_4 ;

les groupes de formule $-(CH_2)_nNR^{19}C(=O)R^{16}$,
dans laquelle :

n et R^{19} sont tels que définis ci-dessus, et R^{16} représente : un atome d'hydrogène ; un groupe alkyle en C_1-C_4 ; un groupe alkyle en C_1-C_4 substitué ayant au moins un substituant choisi parmi les substituants (b), définis ci-dessous ; un groupe hydrocarboné aliphatique en C_2-C_8 ayant une ou deux doubles liaisons carbone-carbone éthyléniquement insaturées, le groupe n'étant pas substitué ou ayant au moins un substituant choisi parmi les substituants (b), définis ci-dessous ; un groupe alcynyle en C_2-C_8 ; un groupe alcynyle en C_2-C_8 substitué ayant au moins un substituant choisi parmi les substituants (b), définis ci-dessous ; un groupe cycloalkyle en C_3-C_8 ; un groupe cycloalkyle en C_3-C_8 substitué ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ; un groupe aryle carbocyclique ayant 6 à 14 atomes de carbone cycliques et n'étant pas substitué ou ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ; ou un groupe hétérocyclique ayant 3 à 6 atomes cycliques dont au moins l'un est un hétéroatome choisi parmi les hétéroatomes d'azote, d'oxygène et de soufre, le groupe hétérocyclique étant monocyclique ou condensé à un ou deux noyaux benzéniques et n'étant pas substitué ou ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ;

les groupes de formule $-(CH_2)_nNR^{19}COCOR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus ;
les groupes de formule $-(CH_2)_nR^{19}COCOOR^{17}$

dans laquelle n et R^{19} sont tels que définis ci-dessus et R^{17} représente un groupe alkyle en C_1-C_4, un groupe cycloalkyle en C_3-C_8 ou un groupe aralkyle ayant 1 à 4 atomes de carbone dans la portion alkyle et 6 à 10 atomes cycliques dans la portion aryle, celle-ci étant un groupe aryle carbocyclique qui n'est pas substitué ou porte au moins un substituant choisi parmi les substituants (c), définis ci-dessous ;
les groupes de formule $-(CH_2)_nNR^{19}CHR^{16}NHCOR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}CHR^{16}NHCONHR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}CHR^{16}NHCOOR^{17}$
dans laquelle n, R^{16}, R^{17} et R^{19} sont tels que définis ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}C(=Y)YR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus et les deux symboles Y sont choisis indépendamment parmi les atomes d'oxygène et de soufre ;
les groupes de formule $-(CH_2)_nNR^{19}C(=Y)NR^{16'}R^{16'}$
dans laquelle n, Y et R^{19} sont tels que définis ci-dessus, et les deux symboles $R^{16'}$ sont choisis indépendamment parmi R^{16}, ou tous deux, avec l'atome d'azote auquel ils sont attachés, forment un groupe hétérocyclique ayant 3 à 7 atomes cycliques dont l'un est l'atome d'azote et dont 0 ou 1 est un hétéroatome supplémentaire choisi parmi des hétéroatomes d'azote, d'oxygène et de soufre ;
les groupes de formule $-(CH_2)_nNR^{19}C(=Y)NR^{16''}NR^{16''}R^{16''}$
dans laquelle n, Y et R^{19} sont tels que définis ci-dessus, et chacun des symboles $R^{16''}$ est choisi indépendamment parmi R^{16}, ou deux quelconques des symboles $R^{16''}$, avec l'atome d'azote auquel chacun est attaché, forme un groupe hétérocyclique ayant 3 à 7 atomes cycliques dont l'un ou deux sont le ou les atomes d'azote et dont 0 ou 1 est un hétéroatome supplémentaire choisi parmi des hétéroatomes d'azote, d'oxygène et de soufre ;
les groupes de formule $-(CH_2)_nNR^{19}C(=Y)NR^{16}NHZ$
dans laquelle n, Y, R^{16} et R^{19} sont tels que définis ci-dessus et Z représente un groupe de formule $-COOR^{17}$, où R^{17} est tel que défini ci-dessus, un groupe de formule $-COR^{16}$, où R^{16} est tel que défini ci-dessus, ou un groupe de formule $-SO_2R^{16}$, où R^{16} est tel que défini ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}C(=NR^{20})NHR^{20}$
dans laquelle n et R^{19} sont tels que définis ci-dessus et les deux symboles R^{20} sont choisis indépendamment parmi R^{16}, les groupes cyano, les groupes nitro, les groupes de formule $-COOR^{17}$, où R^{17} est tel que défini ci-dessus, et les groupes de formule $-COR^{16}$, où R^{16} est tel que défini ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}C(=NR^{20})R^{16}$
dans laquelle n, R^{16}, R^{19} et R^{20} sont tels que définis ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}SO_mR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus et m est 1 ou 2 ;
les groupes de formule $-CONHR^{16}$
dans laquelle R^{16} est tel que défini ci-dessus ; et
les groupes de formule $-COOR^{17}$
dans laquelle R^{17} est tel que défini ci-dessus ;

substituants (a) :

atomes d'halogène, groupes alcoxy en C_1-C_4, groupes alkylthio en C_1-C_4 et groupes alcanoyloxy en C_1-C_5 ;

substituants (b) :

groupes cycloalkyle en C_3-C_8 ; groupes alcoxy en C_1-C_4 ; groupes alkylthio en C_1-C_4 ; groupes cyanoalkylthio en C_2-C_5 ; groupes alcoxycarbonyle en C_2-C_5 ; atomes d'halogènes ; groupes cyano ; groupes nitro ; groupes amino ; groupes aryle carbocycliques ayant 6 à 10 atomes de carbone et n'étant pas substitués ou ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ; groupes hétérocycliques aromatiques ayant 5 à 8 atomes cycliques dont 1 à 4 sont des hétéroatomes choisis parmi des hétéroatomes d'azote, d'oxygène et de soufre, le groupe hétérocyclique étant monocyclique ou condensé à un noyau benzénique ou à un groupe hétérocyclique qui a 5 ou 6 atomes cycliques dont 1 à 3 sont des hétéroatomes d'azote et n'étant pas substitué ou ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ; et groupes aryloxy et arylthio dont la portion aryle compte 6 à 10 atomes de carbone et n'est pas substituée ou porte au moins un substituant choisi parmi les substituants (c),

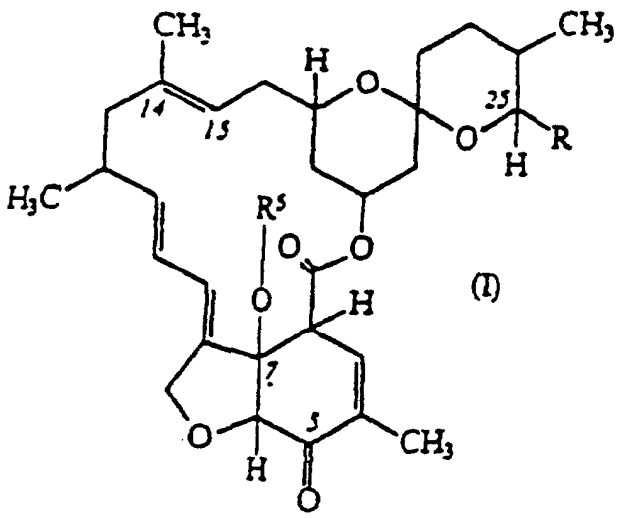
définis ci-dessous ;

substituants (c) :

groupes alkyle en C_1-C_4, groupes alcoxy en C_1-C_4, groupes alkylthio en C_1-C_4, groupes alcanoyloxy en C_1-C_5, groupes alcoxycarbonyle en C_2-C_5, atomes d'halogènes, groupes cyano, groupes nitro, groupes amino, groupes mono- et dialkylamino dans lesquels la ou chaque portion alkyle est en C_1-C_4, groupes carbamoyle, groupes mono- et dialkylcarbamoyle dans lesquels la ou chaque portion alkyle est en C_1-C_4, et groupes alcanoylamino en C_1-C_5 ;

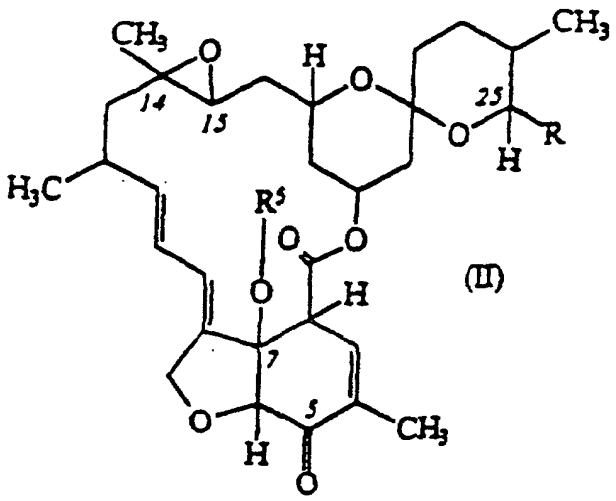
lequel procédé comprend les étapes suivantes :

A. époxyder un composé de formule (I) en utilisant un système de réactifs comprenant des quantités efficaces de peroxymonosulfate de potassium et d'une ou plusieurs cétones :



(I)

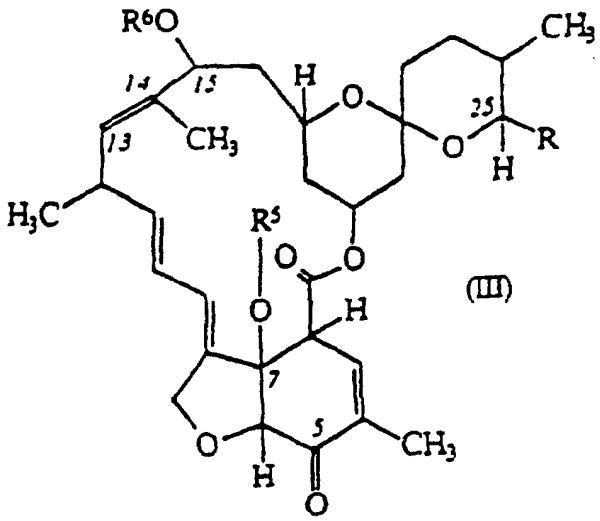
formule dans laquelle R est tel que défini ci-dessus et R^5 représente un atome d'hydrogène ou un groupe de formule $-SiR^2R^3R^4$, où R^2, R^3 et R^4 représentent chacun indépendamment un groupe alkyle ayant 1 à 6 atomes de carbone ;
pour obtenir un composé de formule (II) :



(II)

dans laquelle R et R^5 sont tels que définis ci-dessus ;

B. soumettre le composé résultant de formule (II) à une réaction d'éthérification par ouverture de cycle pour obtenir un composé de formule (III) :



(III)

dans laquelle R et R^5 sont tels que définis ci-dessus et R^6 représente un groupe de formule $-SiR^7R^8R^9$, où R^7, R^8 et R^9 sont chacun indépendamment choisis parmi les groupes alkyle ayant 1 à 6 atomes de carbone, les groupes phényle et les groupes benzyle ; et

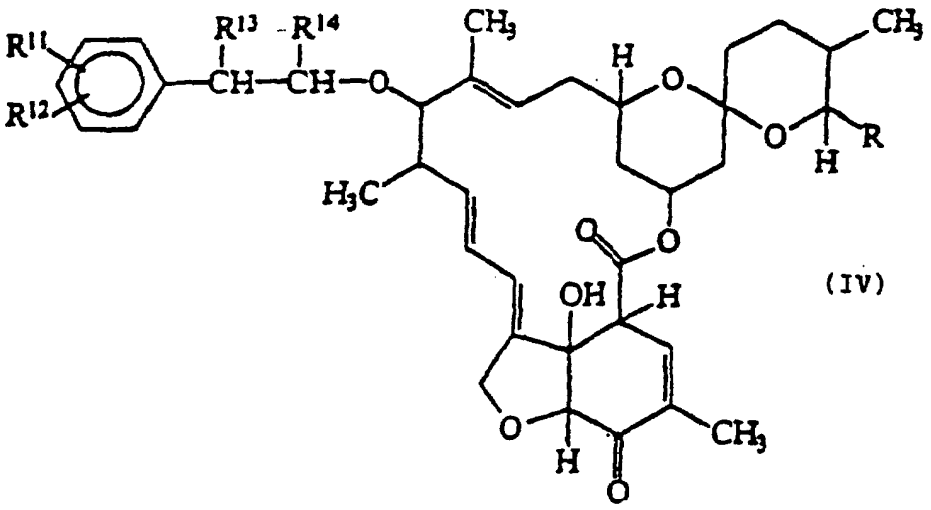
C. faire réagir le composé résultant de formule (III) avec un composé de formule $R^{10}OH$ pour obtenir ledit composé de formule (VIIa).

2. Procédé selon la revendication 1, dans lequel R^5 représente un groupe triméthylsilyle.

3. Procédé selon la revendication 1, dans lequel R^5 représente un atome d'hydrogène.

4. Procédé selon l'une quelconque des revendications précédentes, dans lequel R^{10} représente un groupe 4-(N-méthanesulfonyl-N-méthylamino)phényléthyle.

5. Procédé selon la revendication 1, dans lequel le composé de formule (VIIa) est un composé de formule (IV) :



(IV)

dans laquelle :

R est tel que défini dans la revendication 1,
R^{11} et R^{12} sont choisis indépendamment parmi : les atomes d'hydrogène ; les atomes d'halogènes ; les groupes cyano ; les groupes nitro ; les groupes alkyle en C_1-C_4 ; les groupes alkyle en C_1-C_4 substitués ayant au moins un substituant choisi parmi les substituants (a), définis ci-dessous ; les groupes alcoxy en C_1-C_4 ; les groupes alcoxyalcoxy en C_2-C_6 ;

les groupes de formule $-(CH_2)_nNHR^{19}$,
dans laquelle :

n représente 0 ou le nombre entier 1 ou 2, et R^{19} représente un atome d'hydrogène ou un groupe alkyle en C_1-C_4 ;

les groupes de formule $-(CH_2)_nNR^{19}C(=O)R^{16}$,
dans laquelle :

n et R^{19} sont tels que définis ci-dessus, et
R^{16} représente : un atome d'hydrogène ; un groupe alkyle en C_1-C_4 ; un groupe alkyle en C_1-C_4 substitué ayant au moins un substituant choisi parmi les substituants (b), définis ci-dessous ; un groupe hydrocarboné aliphatique en C_2-C_8 ayant une ou deux doubles liaisons carbone-carbone éthyléniquement insaturées, le groupe n'étant pas substitué ou ayant au moins un substituant choisi parmi les substituants (b), définis ci-dessous ; un groupe alcynyle en C_2-C_8 ; un groupe alcynyle en C_2-C_8 substitué ayant au moins un substituant choisi parmi les substituants (b), définis ci-dessous ; un groupe cycloalkyle en C_3-C_8 ; un groupe cycloalkyle en C_3-C_8 substitué ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ; un groupe aryle carbocyclique ayant 6 à 14 atomes de carbone cycliques et n'étant pas substitué ou ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ; ou un groupe hétérocyclique ayant 3 à 6 atomes cycliques dont au moins l'un est un hétéroatome choisi parmi les hétéroatomes d'azote, d'oxygène et de soufre, le groupe hétérocyclique étant monocyclique ou condensé à un ou deux noyaux benzéniques et n'étant pas substitué ou ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ;

les groupes de formule $-(CH_2)_nNR^{19}COCOR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus ;
les groupes de formule $-(CH_2)_nR^{19}COCOOR^{17}$
dans laquelle n et R^{19} sont tels que définis ci-dessus et R^{17} représente un groupe alkyle en C_1-C_4, un groupe cycloalkyle en C_3-C_8 ou un groupe aralkyle tel que défini ci-dessous ;
les groupes de formule $-(CH_2)_nNR^{19}CHR^{16}NHCOR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus ;

les groupes de formule-$(CH_2)_nNR^{19}CHR^{16}NHCONHR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}CHR^{16}NHCOOR^{17}$
dans laquelle n, R^{16}, R^{17} et R^{19} sont tels que définis ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}C(=Y)YR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus et les deux symboles Y sont choisis indépendamment parmi les atomes d'oxygène et de soufre ;
les groupes de formule $-(CH_2)_nNR^{19}C(=Y)NR^{16'}R^{16'}$
dans laquelle n, Y et R^{19} sont tels que définis ci-dessus, et les deux symboles $R^{16'}$ sont choisis indépendamment parmi R^{16}, ou tous deux, avec l'atome d'azote auquel ils sont attachés, forment un groupe hétérocyclique ayant 3 à 7 atomes cycliques dont l'un est l'atome d'azote et dont 0 ou 1 est un autre hétéroatome choisi parmi des hétéroatomes d'azote, d'oxygène et de soufre ;
les groupes de formule $-(CH_2)_nNR^{19}C(=Y)NR^{16"}NR^{16"}R^{16"}$
dans laquelle n, Y et R^{19} sont tels que définis ci-dessus, et chacun des symboles $R^{16"}$ est choisi indépendamment parmi R^{16}, ou deux quelconques des symboles $R^{16"}$, avec l'atome d'azote auquel chacun est attaché, forme un groupe hétérocyclique ayant 3 à 7 atomes cycliques dont l'un ou deux sont le ou les atomes d'azote et dont 0 ou 1 est un autre hétéroatome choisi parmi des hétéroatomes d'azote, d'oxygène et de soufre ;
les groupes de formule $-(CH_2)_nNR^{19}C(=Y)NR^{16}NHZ$
dans laquelle n, Y, R^{16} et R^{19} sont tels que définis ci-dessus et Z représente un groupe de formule $-COOR^{17}$, où R^{17} est tel que défini ci-dessus, un groupe de formule $-COR^{16}$, où R^{16} est tel que défini ci-dessus, ou un groupe de formule $-SO_2R^{16}$, où R^{16} est tel que défini ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}C(=NR^{20})NHR^{20}$
dans laquelle n et R^{19} sont tels que définis ci-dessus et les deux symboles R^{20} sont choisis indépendamment parmi R^{16}, les groupes cyano, les groupes nitro, les groupes de formule $-COOR^{17}$, où R^{17} est tel que défini ci-dessus, et les groupes de formule $-COR^{16}$, où R^{16} est tel que défini ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}C(=NR^{20})R^{16}$
dans laquelle n, R^{16}, R^{19} et R^{20} sont tels que définis ci-dessus ;
les groupes de formule $-(CH_2)_nNR^{19}SO_mR^{16}$
dans laquelle n, R^{16} et R^{19} sont tels que définis ci-dessus et m est 1 ou 2 ;
les groupes de formule $-CONHR^{16}$
dans laquelle R^{16} est tel que défini ci-dessus ; et
les groupes de formule $-COOR^{17}$
dans laquelle R^{17} est tel que défini ci-dessus ; et
R^{13} et R^{14} sont choisis indépendamment parmi les atomes d'hydrogène, les groupes alkyle en C_1-C_4 et les groupes alcoxy en C_1-C_4 ;
les groupes aralkyle ont 1 à 4 atomes de carbone dans la portion alkyle et 6 à 10 atomes cycliques dans la portion aryle, celle-ci étant un groupe aryle carbocyclique qui n'est pas substitué ou porte au moins un substituant choisi parmi les substituants (c), définis ci-dessous ;

substituants (a) :

atomes d'halogène, groupes alcoxy en C_1-C_4, groupes alkylthio en C_1-C_4 et groupes alcanoyloxy en C_1-C_5 ;

substituants (b) :

groupes cycloalkyle en C_3-C_8 ; groupes alcoxy en C_1-C_4 ; groupes alkylthio en C_1-C_4 ; groupes cyanoalkylthio en C_2-C_5 ; groupes alcoxycarbonyle en C_2-C_5 ; atomes d'halogènes ; groupes cyano ; groupes nitro ; groupes amino ; groupes aryle carbocycliques ayant 6 à 10 atomes de carbone et n'étant pas substitués ou ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ; groupes hétérocycliques aromatiques ayant 5 à 8 atomes cycliques dont 1 à 4 sont des hétéroatomes choisis parmi des hétéroatomes d'azote, d'oxygène et de soufre, le groupe hétérocyclique étant monocyclique ou condensé à un noyau benzénique ou à un groupe hétérocyclique qui a 5 ou 6 atomes cycliques dont 1 à 3 sont des hétéroatomes d'azote et n'étant pas substitué ou ayant au moins un substituant choisi parmi les substituants (c), définis ci-dessous ; et groupes aryloxy et arylthio dont la portion aryle compte 6 à 10 atomes de carbone et n'est pas substituée ou porte au moins un substituant choisi parmi les substituants (c), définis ci-dessous ;

substituants (c) :

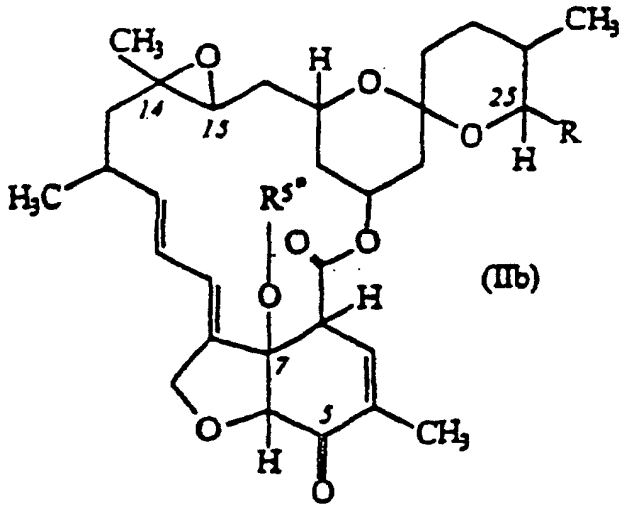
groupes alkyle en C_1-C_4, groupes alcoxy en C_1-C_4, groupes alkylthio en C_1-C_4, groupes alcanoyloxy en C_1-C_5, groupes alcoxycarbonyle en C_2-C_5, atomes d'halogènes, groupes cyano, groupes nitro, groupes amino, groupes mono- et dialkylamino dans lesquels la ou chaque portion alkyle est en C_1-C_4, groupes carbamoyle, groupes mono- et dialkylcarbamoyle dans lesquels la ou chaque portion alkyle est en C_1-C_4, et groupes alcanoylamino en C_1-C_5 ;

et les sels de celui-ci.

6. Procédé selon l'une quelconque des revendications précédentes, dans lequel le composé de formule (IV) ou (VIIa) est encore hydrogéné pour donner un composé ayant un groupe hydroxyle à la position 5.

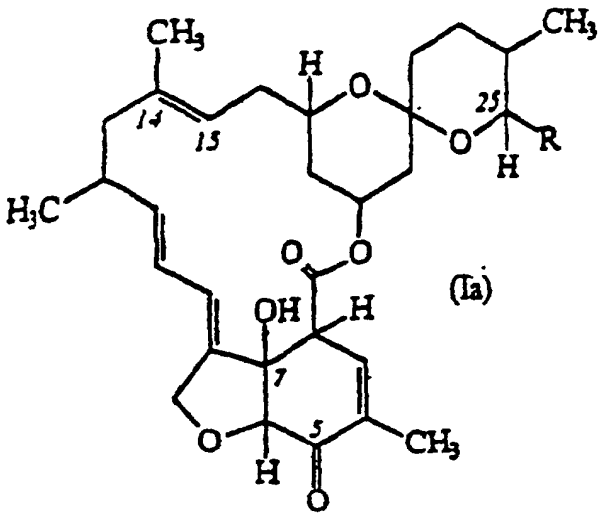
7. Procédé selon la revendication 6, dans lequel le composé de formule (IV) ou (VIIa) est la 5-oxo-13-{2-[4-(N-méthanesulfonyl-N-méthylamino)phényl]éthoxy}milbémycine A_4 et est encore hydrogéné pour donner la 13-{2-[4-(N-méthanesulfonyl-N-méthylamino)phényl]éthoxy}milbémycine A_4.

8. Procédé pour la préparation d'un composé de formule (IIb) :



(IIb)

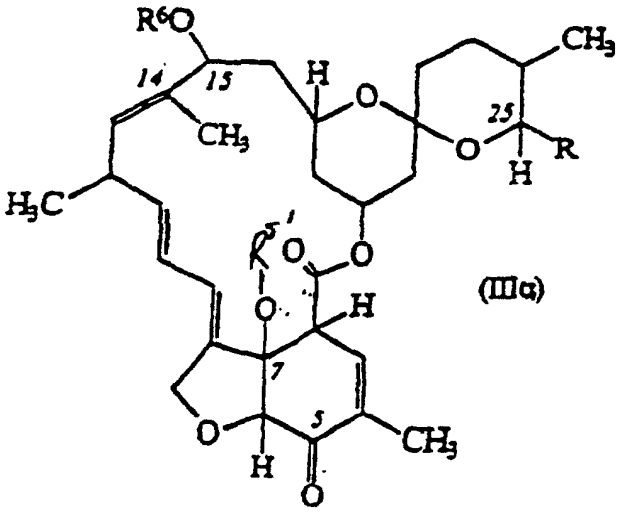
dans laquelle R est tel que défini dans la revendication 1 ; et $R^{5"}$ représente un atome d'hydrogène ; lequel procédé comprend l'époxydation d'un composé de formule (Ia) :



(Ia)

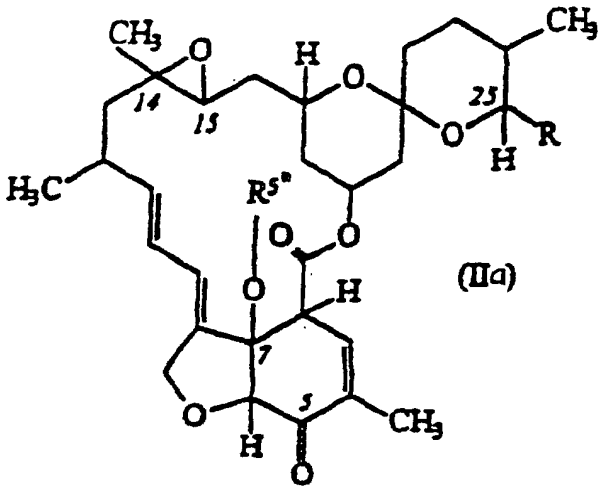
dans laquelle R est tel que défini ci-dessus, ladite époxydation étant effectuée par un système de réactifs comprenant des quantités efficaces de peroxymonosulfate de potassium et d'une ou plusieurs cétones.

9. Procédé pour la préparation d'un composé de formule (IIIa) :



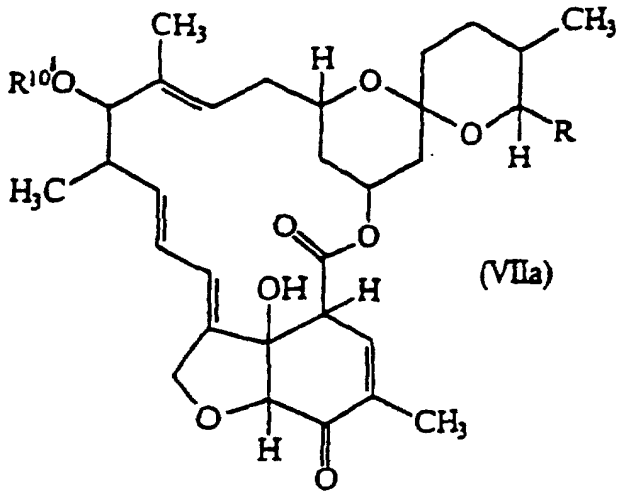
(IIIa)

dans laquelle R est tel que défini dans la revendication 1, $R^{5'}$ représente un groupe de formule $-SiR^2R^3R^4$, où R^2, R^3 et R^4 représentent chacun indépendamment un groupe alkyle ayant 1 à 4 atomes de carbone, et R^6 représente un groupe de formule $SiR^7R^8R^9$, où R^7 est choisi parmi les groupes alkyle ayant 1 à 4 atomes de carbone et R^8 et R^9 sont choisis chacun indépendamment parmi les groupes alkyle ayant 1 à 4 atomes de carbone, les groupes phényle et les groupes benzyle ;
lequel procédé comprend l'étape consistant à soumettre un composé de formule (IIa) :

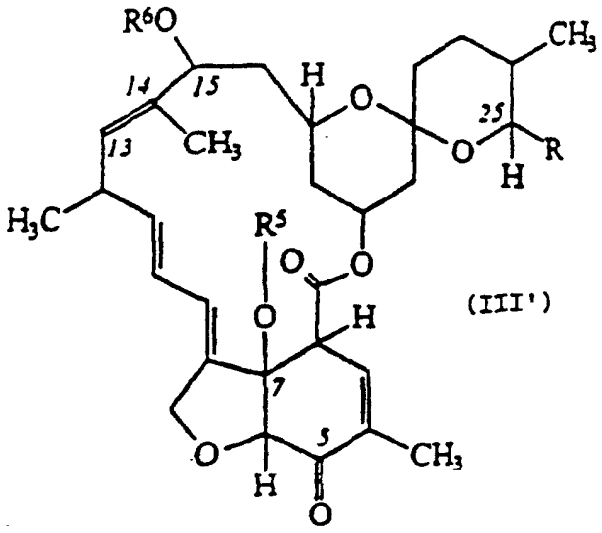


dans laquelle R et $R^{5'}$ sont tels que définis ci-dessus ; à une réaction d'éthérification par ouverture de cycle.

10. Procédé pour la préparation d'un composé de formule (VIIa) :



dans laquelle R est tel que défini dans la revendication 1 et $R^{10'}$ représente un groupe 4-(N-méthanesulfonyl-N-méthylamino)phényléthyle,
lequel procédé comprend la réaction d'un composé de formule (III') :



dans laquelle R est tel que défini dans la revendication 1, R^5 représente un atome d'hydrogène ou un groupe de formule $-SiR^2R^3R^4$ où R^2, R^3 et R^4 representent chacun indépendamment un groupe alkyle ayant 1 à 4 atomes de carbone ; et R^6 représente un atome d'hydrogène ou un groupe de formule $-SiR^7R^8R^9$ où R^7 est choisi parmi les groupes alkyle ayant 1 à 4 atomes de carbone et R^8 et R^9 sont choisis chacun indépendamment parmi les groupes alkyle ayant 1 à 4 atomes de carbone, les groupes phényle et les groupes benzyle, avec un composé de formule $R^{10'}OH$ en présence d'un acide.

11. Procédé selon la revendication 10, dans lequel le composé de formule (VIIa) est encore hydrogéné pour donner un composé ayant un groupe hydroxyle à la position 5.

12. Procédé selon la revendication 10 ou la revendication 11, dans lequel R^5 représente un atome d'hydrogène.

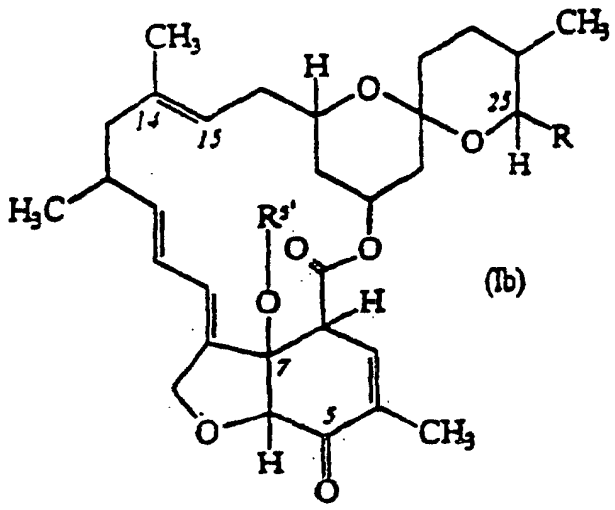
13. Procédé selon la revendication 10 ou la revendication 11, dans lequel R^5 représente un groupe triméthylsilyle.

14. Procédé selon l'une quelconque des revendications précédentes, dans lequel R^6 représente un groupe triméthylsilyle.

15. Procédé selon l'une quelconque des revendications 1 à 7 et 9 à 14, dans lequel R représente un groupe méthyle ou un groupe éthyle.

16. Procédé selon l'une quelconque des revendications 1 à 8 et 11 à 15, dans lequel le composé de formule (VIIa) est la 5-oxo-13-{2-[4-(N-méthanesulfonyl-N-méthylamino)phényl]éthoxy}milbémycine A_4 et est encore hydrogéné pour donner la 13-{2-[4-(N-méthanesulfonyl-N-méthylamino)-phényl]éthoxy}milbémycine A_4.

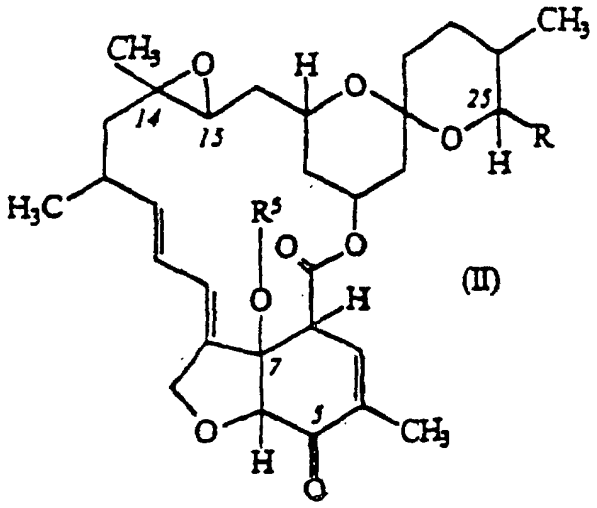
17. Composé de formule (Ib) :



dans laquelle R représente un groupe méthyle, un groupe éthyle, un groupe isopropyle ou un groupe sec-butyle, et $R^{5'}$ représente un groupe de formule $-SiR^2R^3R^4$ où R^2, R^3 et R^4 représentent chacun indépendamment un groupe alkyle ayant 1 à 4 atomes de carbone.

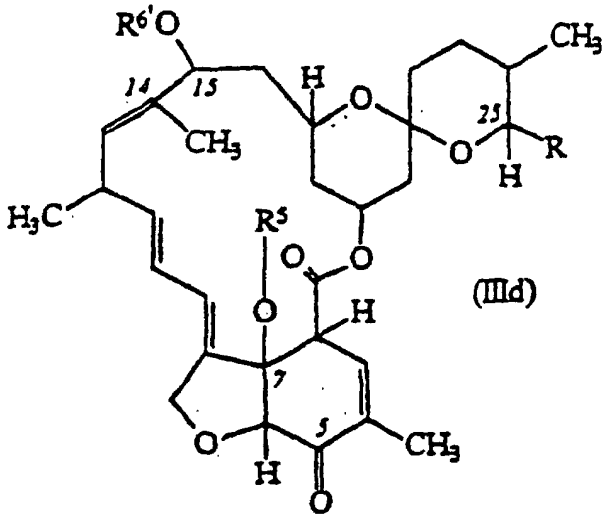
18. Composé selon la revendication 17, dans lequel $R^{5'}$ représente un groupe triméthylsilyle.

19. Composé de formule (II) :



dans laquelle R représente un groupe méthyle, un groupe éthyle, un groupe isopropyle ou un groupe *sec*-butyle, et R^5 représente un atome d'hydrogène ou un groupe de formule $-SiR^2R^3R^4$ où R^2, R^3 et R^4 représentent chacun indépendamment un groupe alkyle ayant 1 à 4 atomes de carbone.

20. Composé de formule (IIId) :



(IIId)

dans laquelle R représente un groupe méthyle, un groupe éthyle, un groupe isopropyle ou un groupe *sec*-butyle, R^5 représente un atome d'hydrogène ou un groupe de formule $-SiR^2R^3R^4$ où R^2, R^3 et R^4 représentent chacun indépendamment un groupe alkyle ayant 1 à 4 atomes de carbone, et $R^{6'}$ représente un atome d'hydrogène ou un groupe de formule $-SiR^7R^8R^9$ où R^7 est choisi parmi les groupes alkyle ayant 1 à 4 atomes de carbone et R^8 et R^9 sont choisis chacun indépendamment parmi les groupes alkyle ayant 1 à 4 atomes de carbone, les groupes phényle et les groupes benzyle.

21. Composé selon la revendication 19 ou 20, dans lequel R^5 représente un groupe de formule $-SiR^2R^3R^4$ où R^2, R^3 et R^4 représentent chacun indépendamment un groupe alkyle ayant 1 à 4 atomes de carbone.

22. Composé selon la revendication 21, dans lequel R^5 représente un groupe triméthylsilyle.

23. Composé selon la revendication 19 ou 20, dans lequel R^5 représente un atome d'hydrogène.

24. Composé selon l'une quelconque des revendications 20 à 23, dans lequel $R^{6'}$ représente un groupe de formule $-SiR^7R^8R^9$ où R^7 est choisi parmi les groupes alkyle ayant 1 à 4 atomes de carbone, et R^8 et R^9 sont choisis chacun indépendamment parmi les groupes alkyle ayant 1 à 4 atomes de carbone, les groupes phényle et les groupes benzyle.

25. Composé selon la revendication 24, dans lequel $R^{6'}$ représente un groupe triméthylsilyle.

26. Composé selon l'une quelconque des revendications 17 à 25, dans lequel R représente un groupe méthyle ou un groupe éthyle.